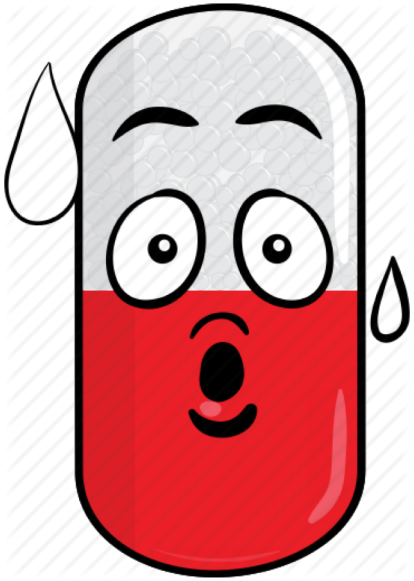
Inteligencia Artificial en el desarrollo de fármacos.
O cómo ser un fármaco y no morir en el intento



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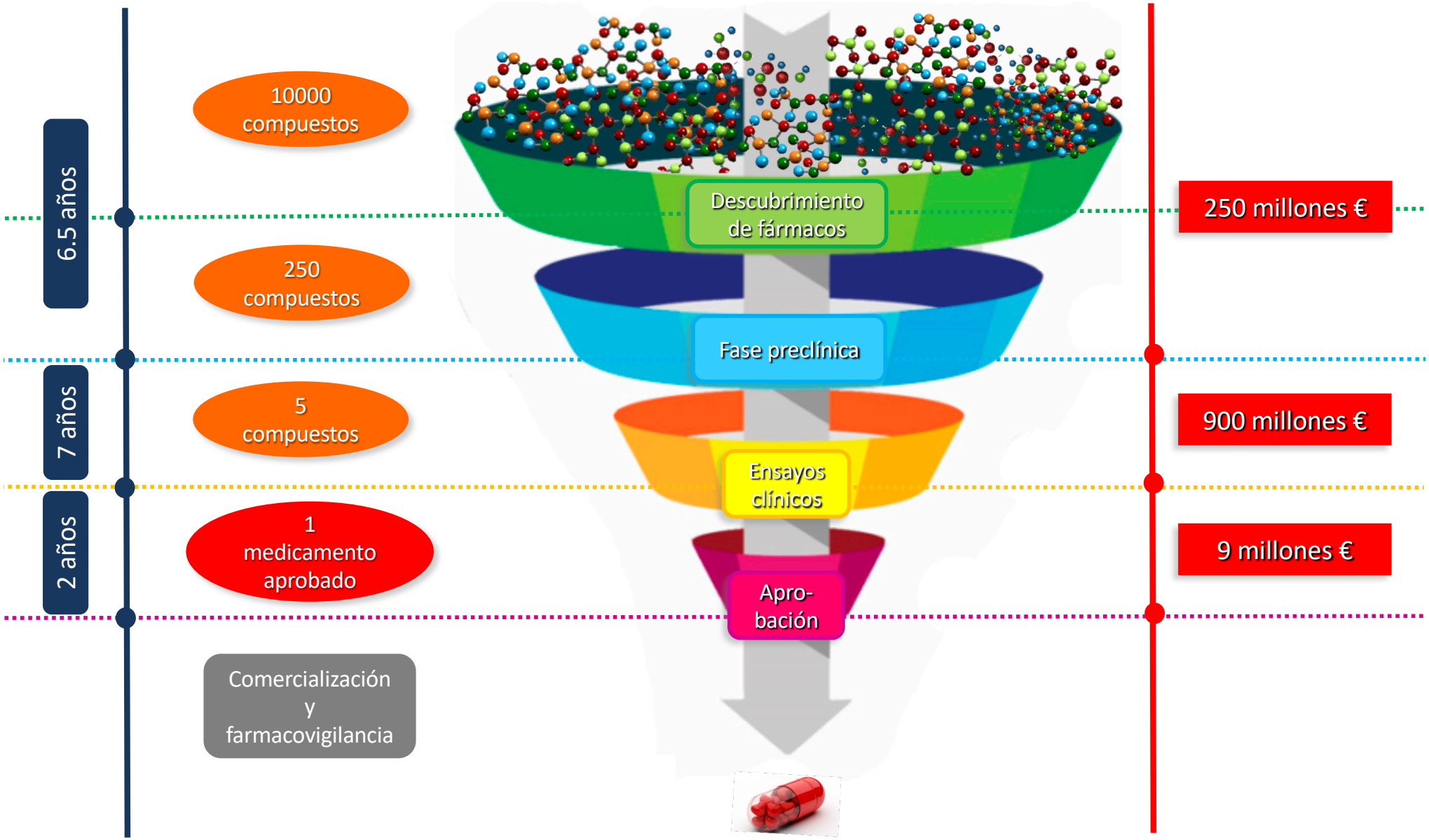
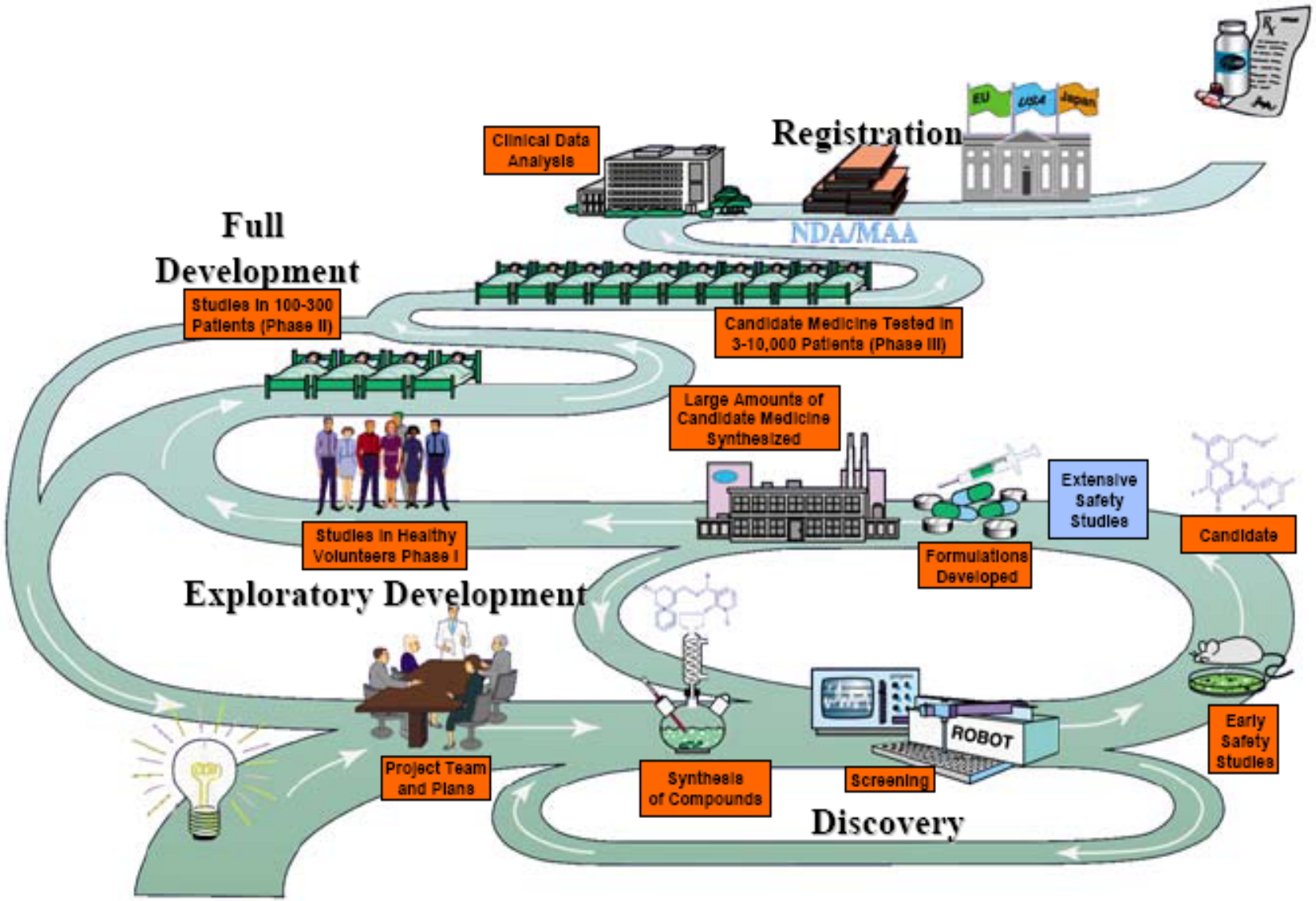
@nuriaecam45

Drug development: Time and Cost

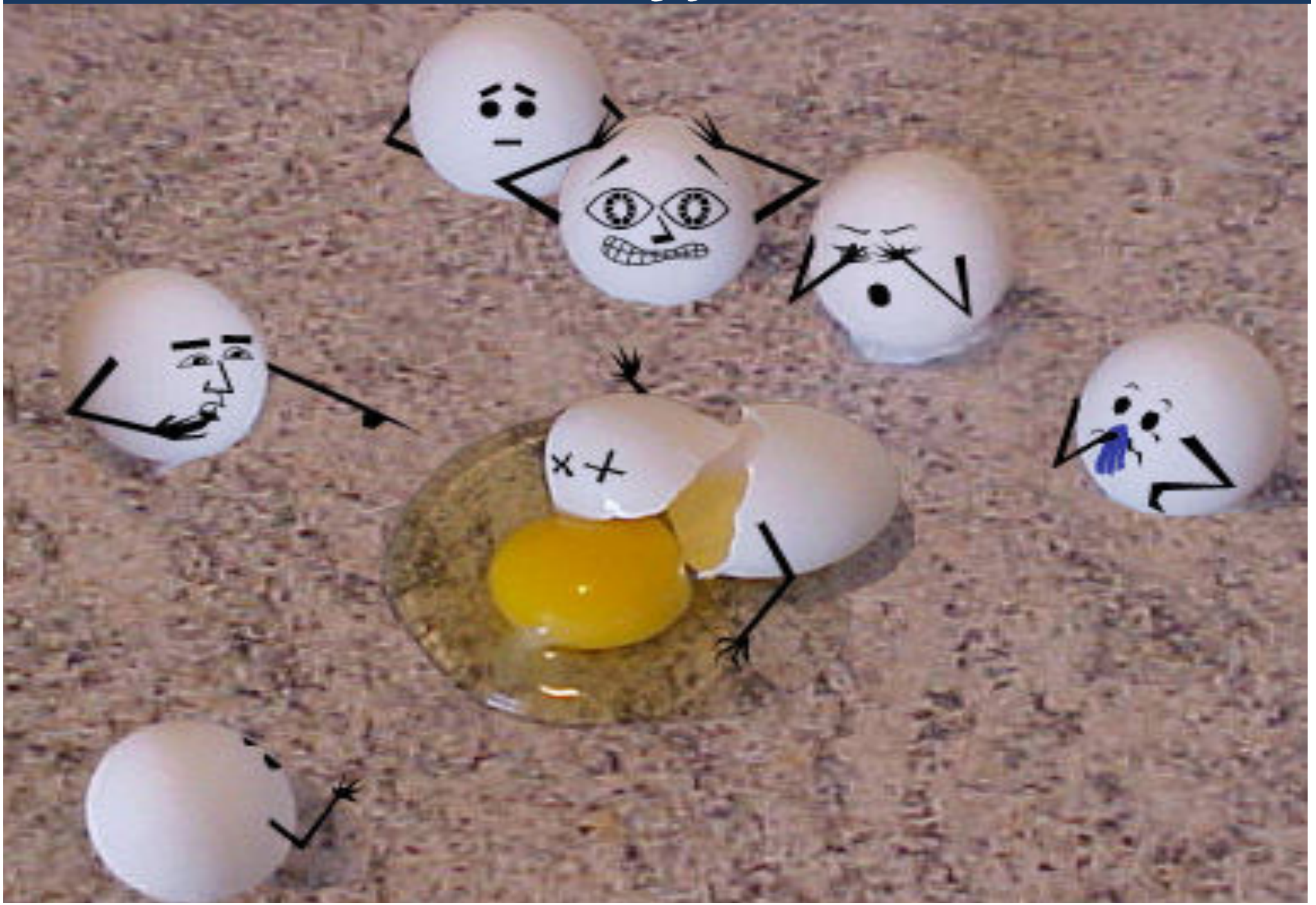


Complex and long travel

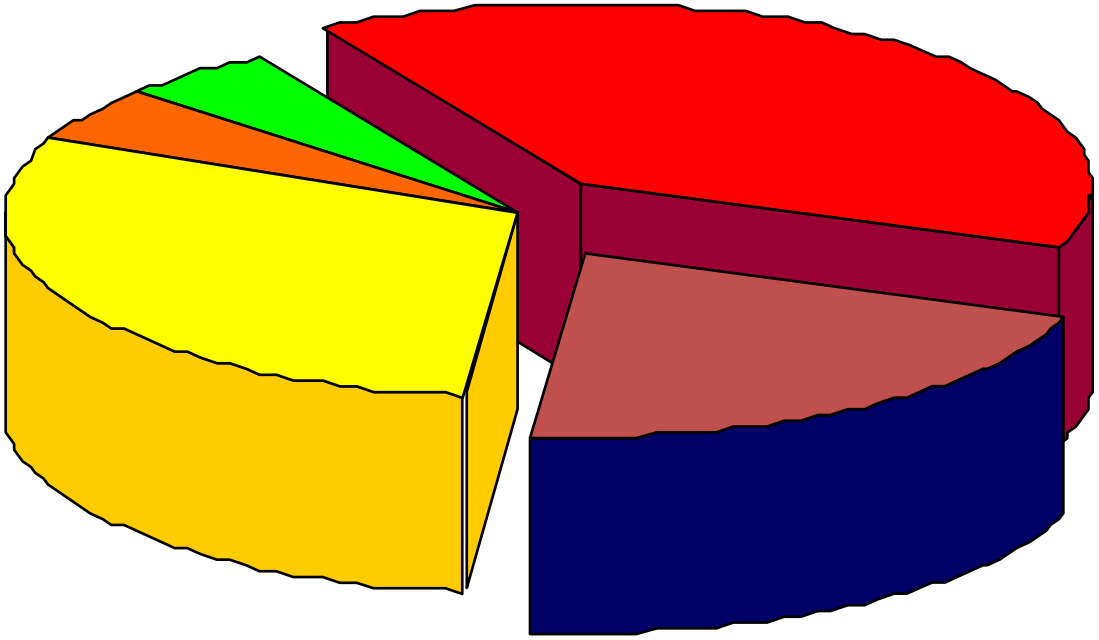


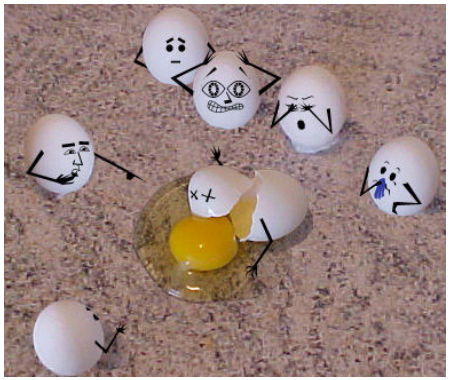
Development of new drugs

Too many failures



Too many failures





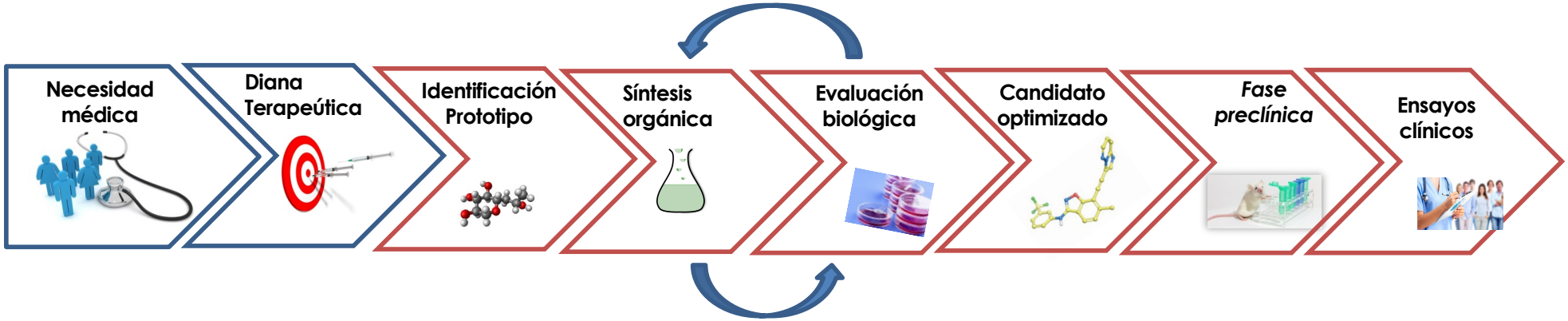
- Pharmacokinetic properties
- Toxicity
- Loss of efficacy
- Bussiness reasons
- Various

60% ADMET

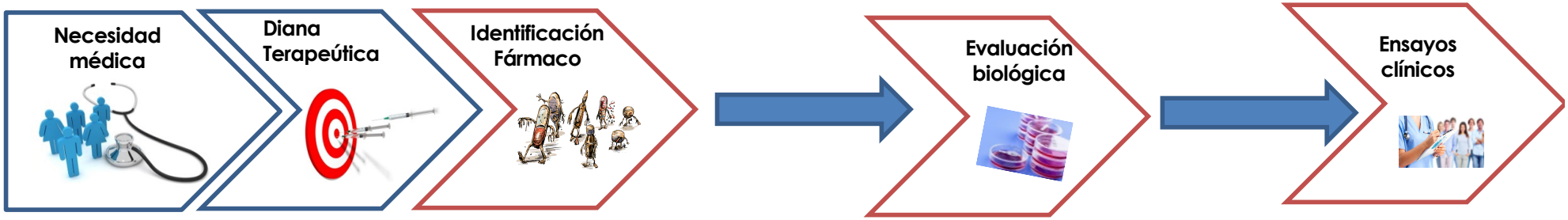
- Absorption
- Distribution
- Metabolism
- Excretion
- Toxicity

Drug development

- Desarrollo tradicional

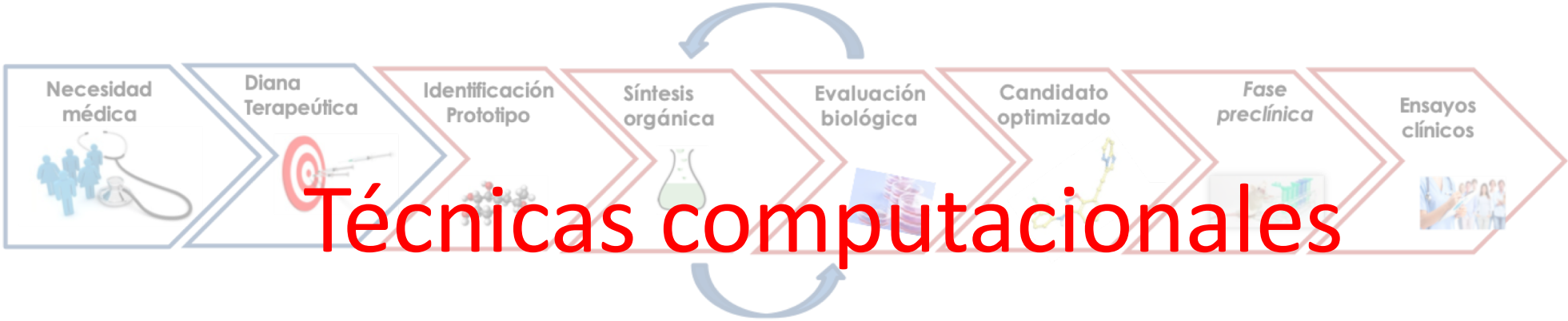


- Reposicionamiento de fármacos



Drug development

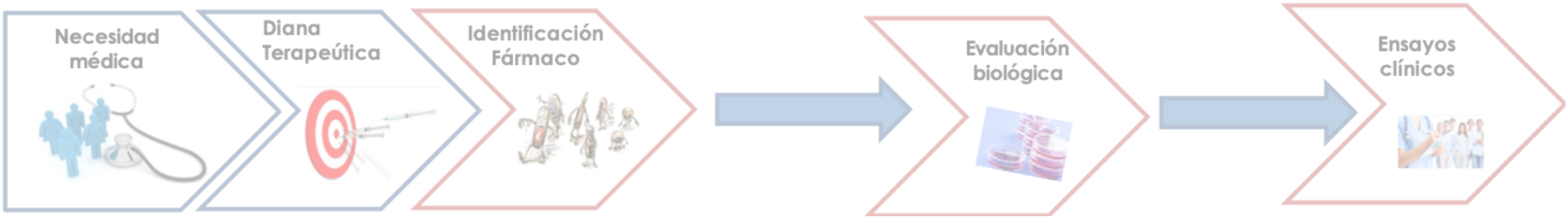
- Desarrollo tradicional



Técnicas computacionales

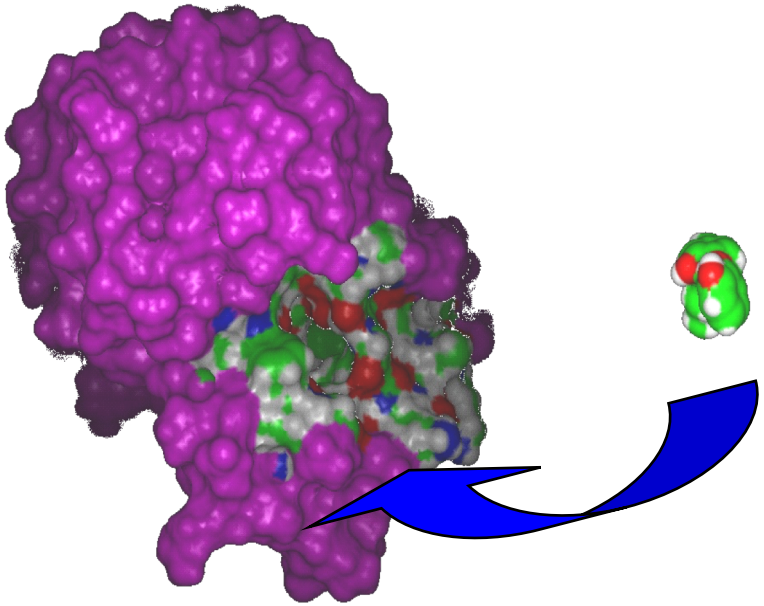
- Reposicionamiento de fármacos

Inteligencia Artificial

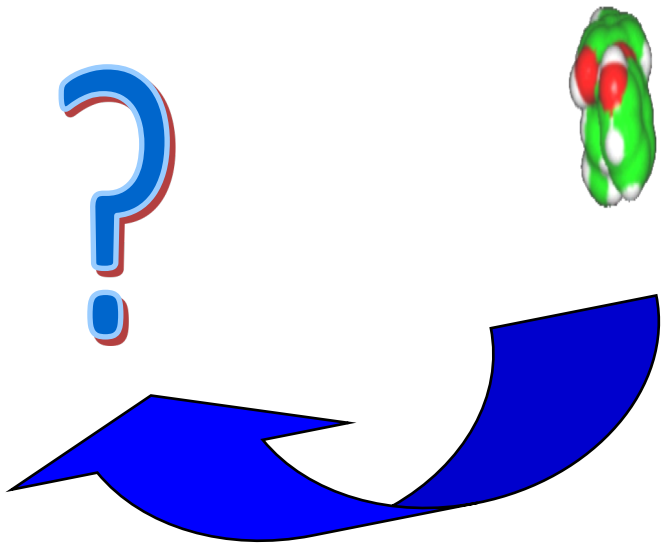


Computational Strategies

TARGET-BASED

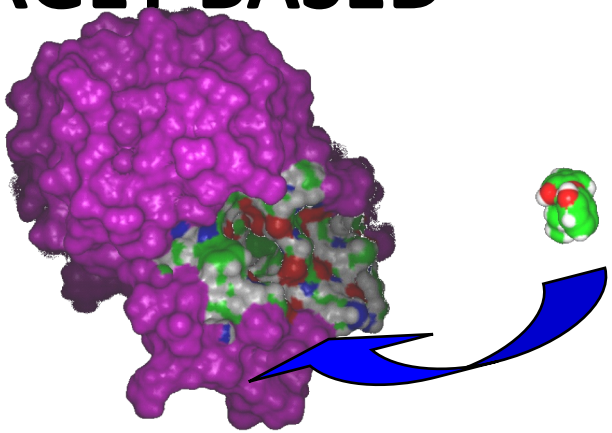


LIGAND-BASED

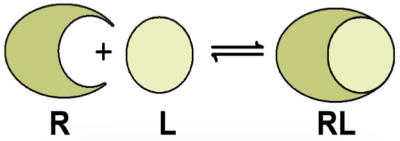


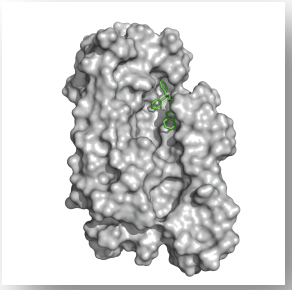
Computational Strategies

TARGET-BASED

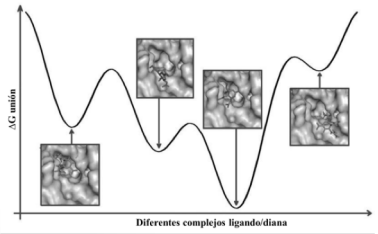


Ligand Docking

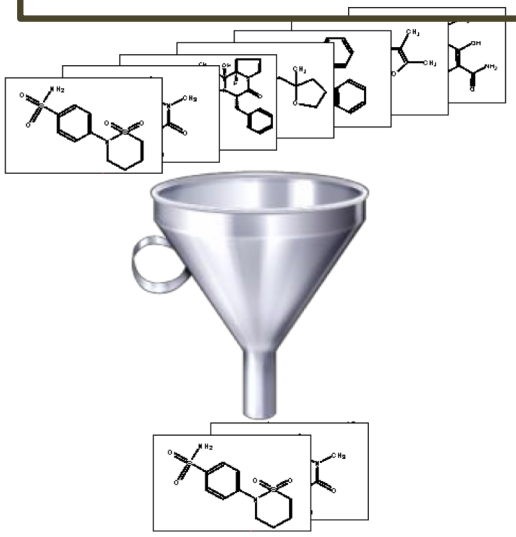


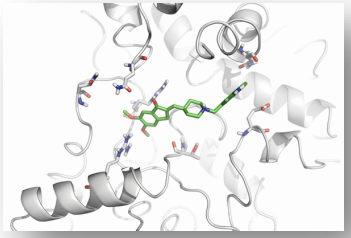


De novo desing



Virtual screening

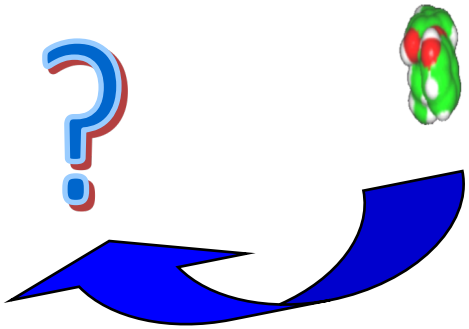




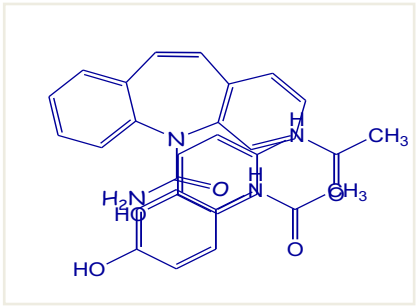
Molecular dynamics

Computational Strategies

LIGAND-BASED



Descriptors



QSA/PR

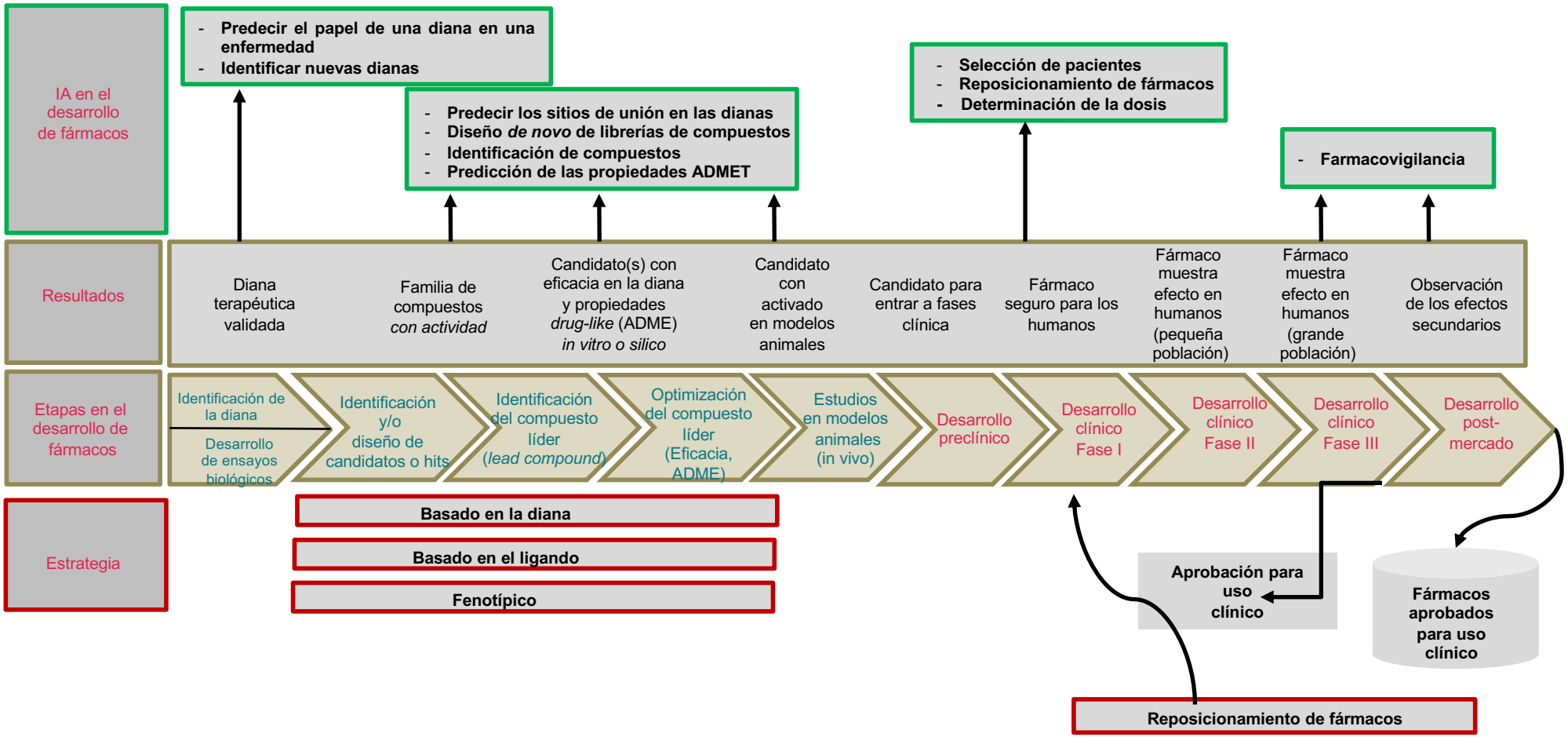
$y=f(x)$

Artificial Intelligence

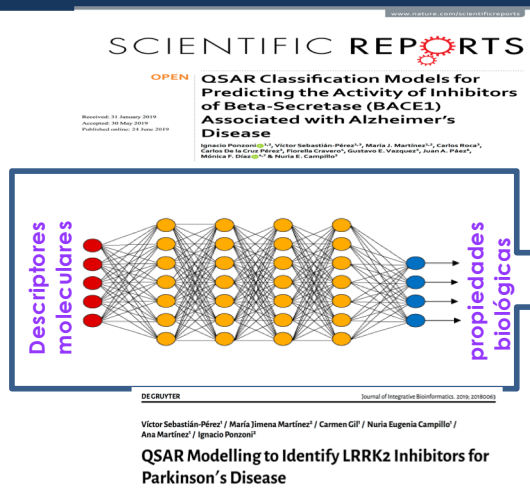
Dataset of molecules (actives/no actives)

Experimental data (biological or physico-chemical properties)

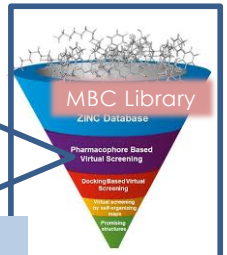
IA in drug development



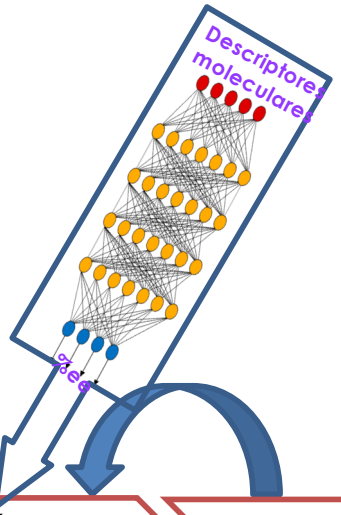
Research Projects

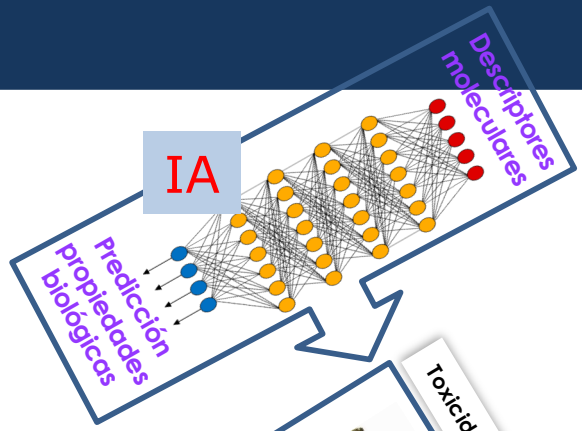


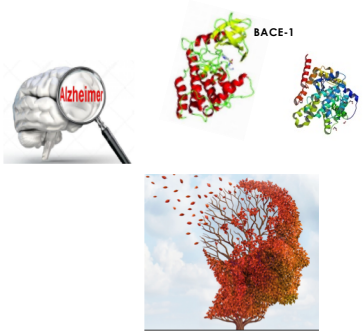
Cribado virtual



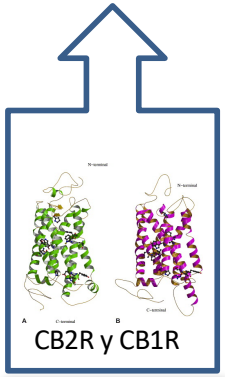
IA



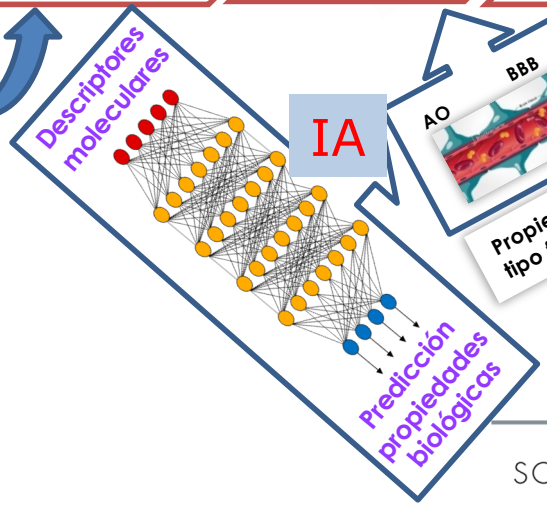




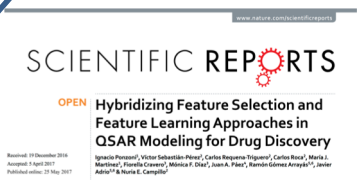
Enfermedad de Alzheimer



Diseño racional



IA



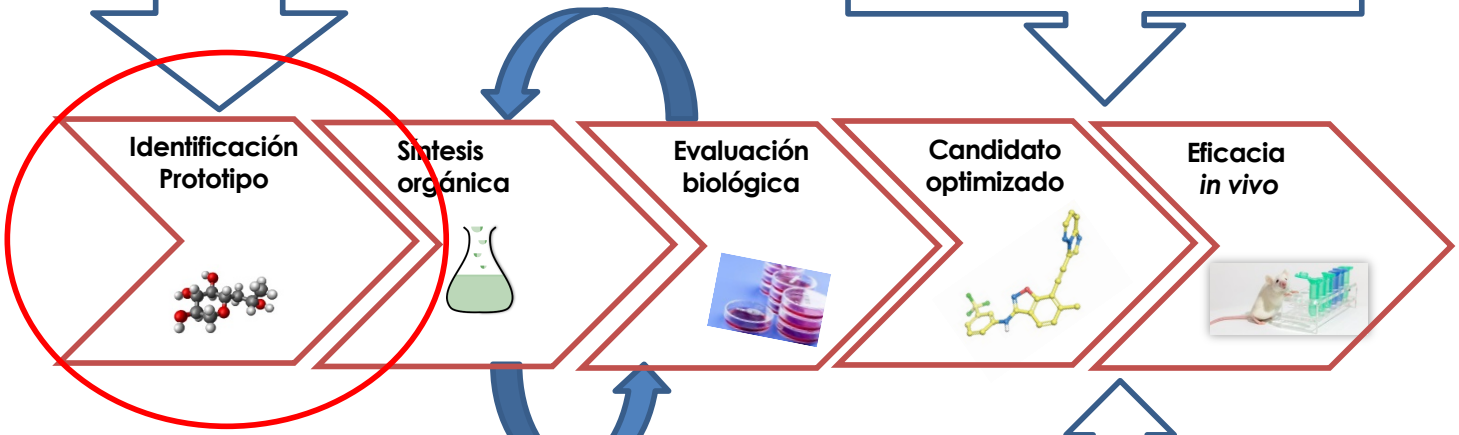
IA in drug development

Identificación prototipo

✓ Modelo Predictivo Machine Learning (ML)
(Actividad BACE-1)
✓ Modelo Predictivo ML
(Actividad LRRK2)
En proceso Modelo Predictivo Deep Learning (DL)
(Actividad Cannabinoide (CB2/CB1)
En proceso Modelo Predictivo Deep Learning (DL)
(Actividad Leishmaniasis)

Toxicidad

En proceso diferentes Modelos Predicitovs DL
(Toxicidad)
(Mutagenesis. Test Ames)

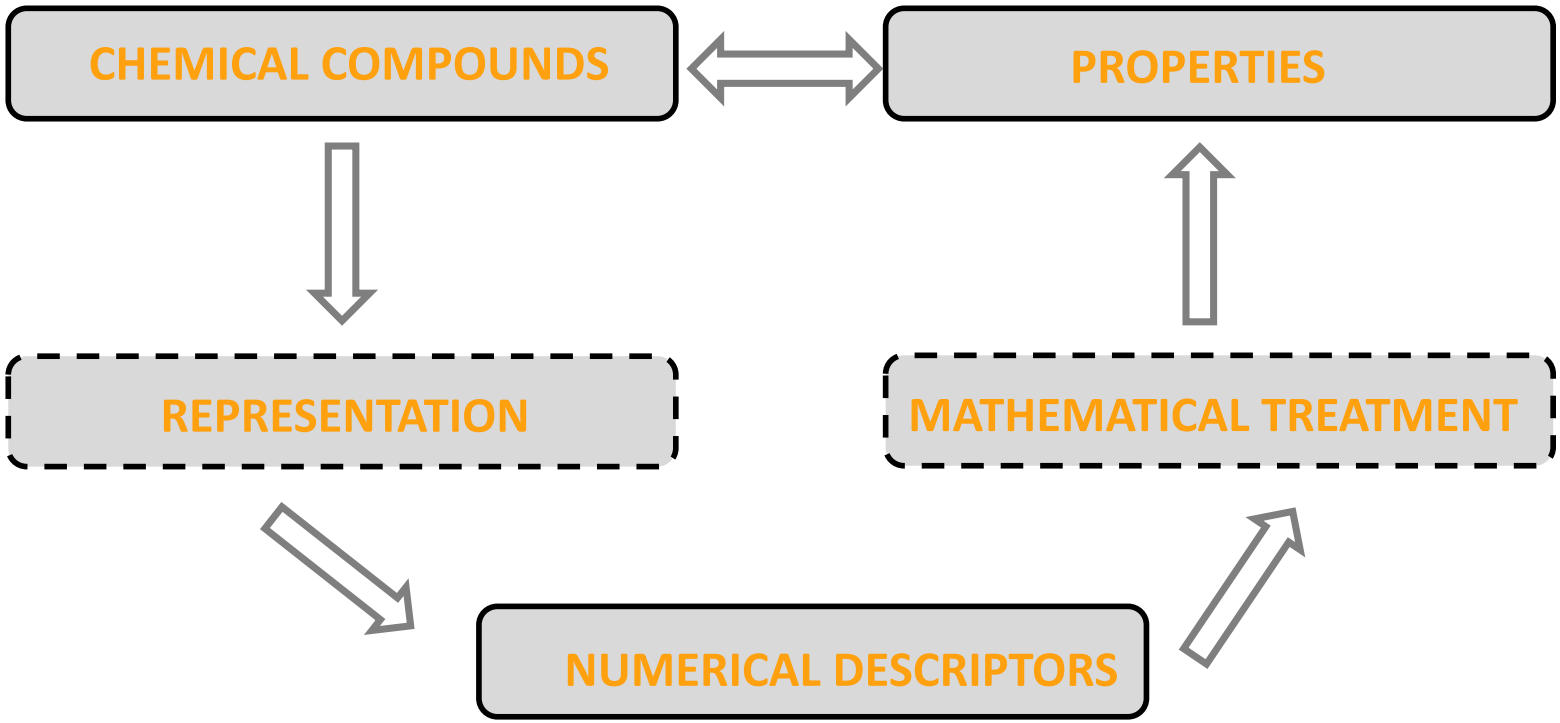


✓ Modelo Predictivo ML **(%ee)**

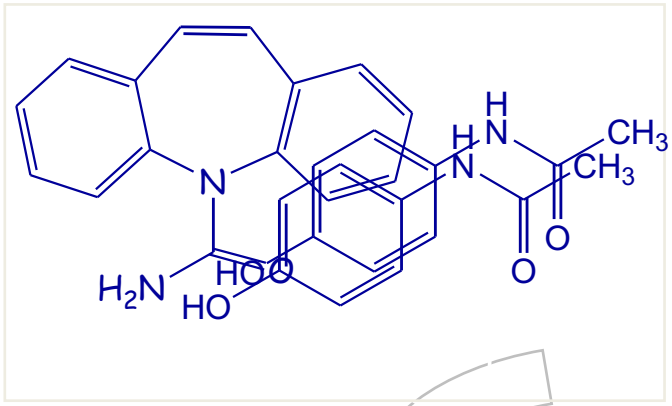
✓ Modelo Predictivo ML **(HIA%)**
✓ Modelo Predictivo ML **(BBB%)**

Propiedades tipo fármaco

IA in drug development



IA in drug development



Biological properties

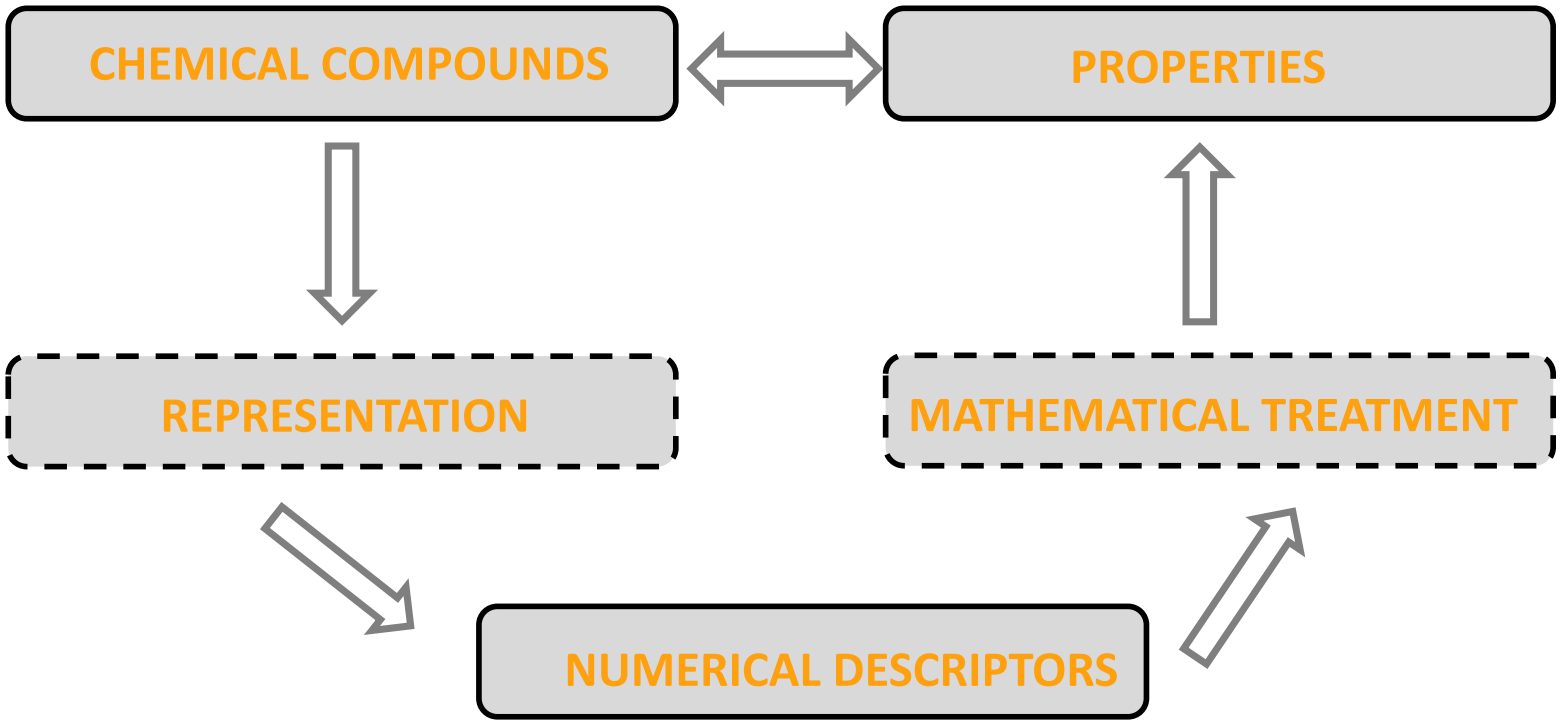
"Numerical definition or codification"

Molecular descriptors:

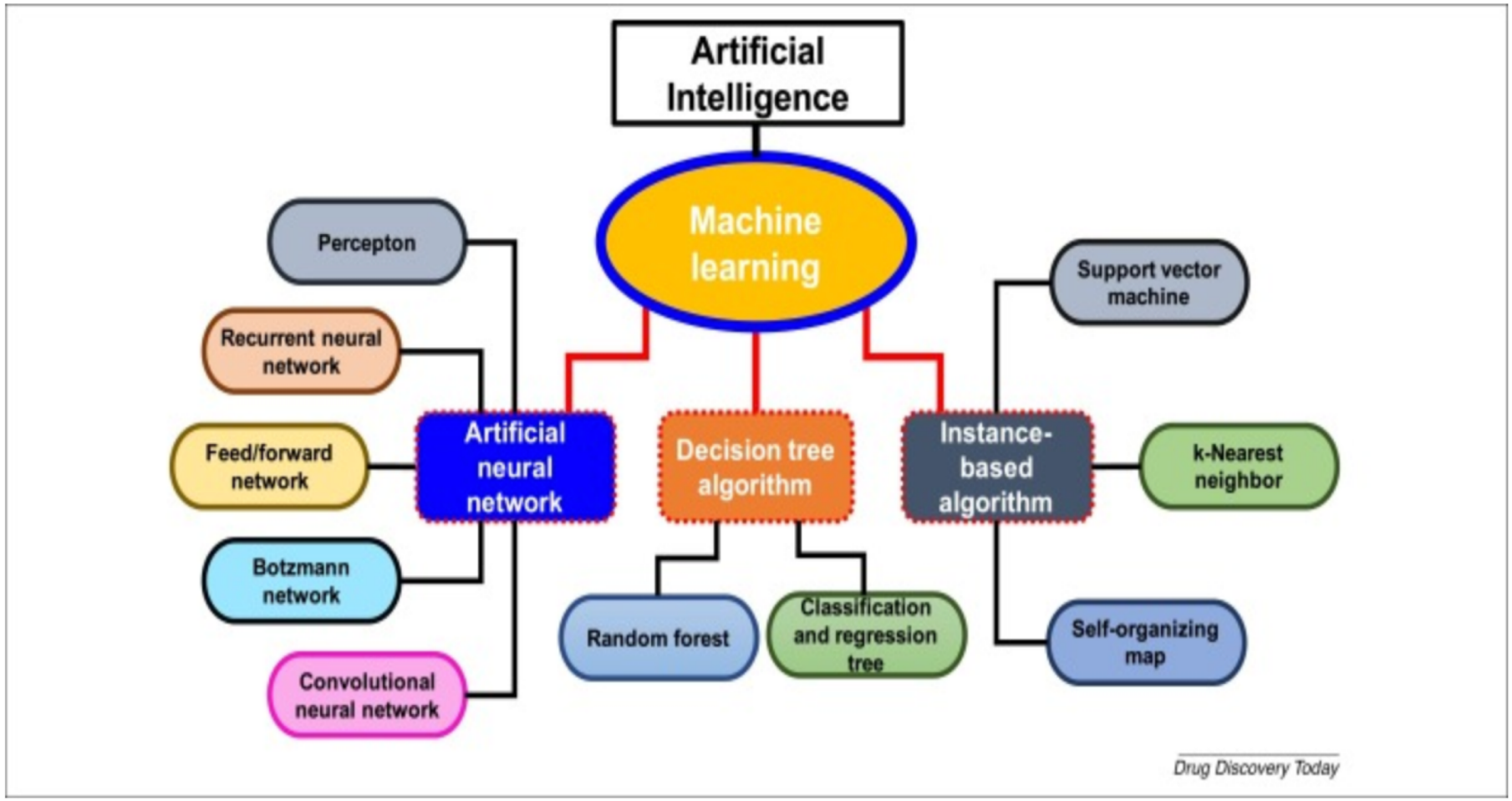
1. **Physicochemical**
2. **Topologicals**
3. **Structurals**
4. **Geometrics**

Set of parameters that unequivocally describe each structure and explain how the different biological properties are affected as a function of these parameters.

IA in drug development

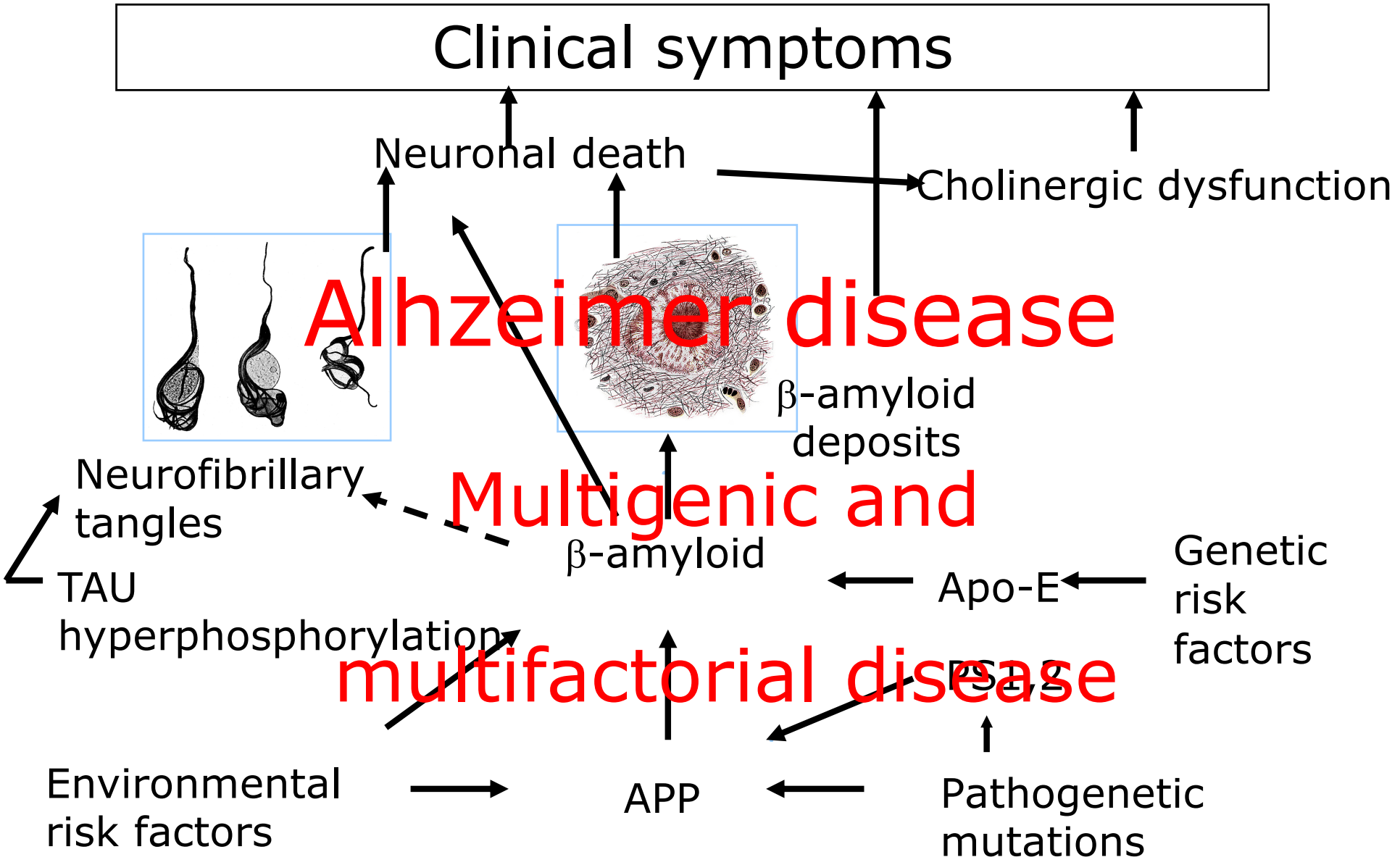


Methods of AI

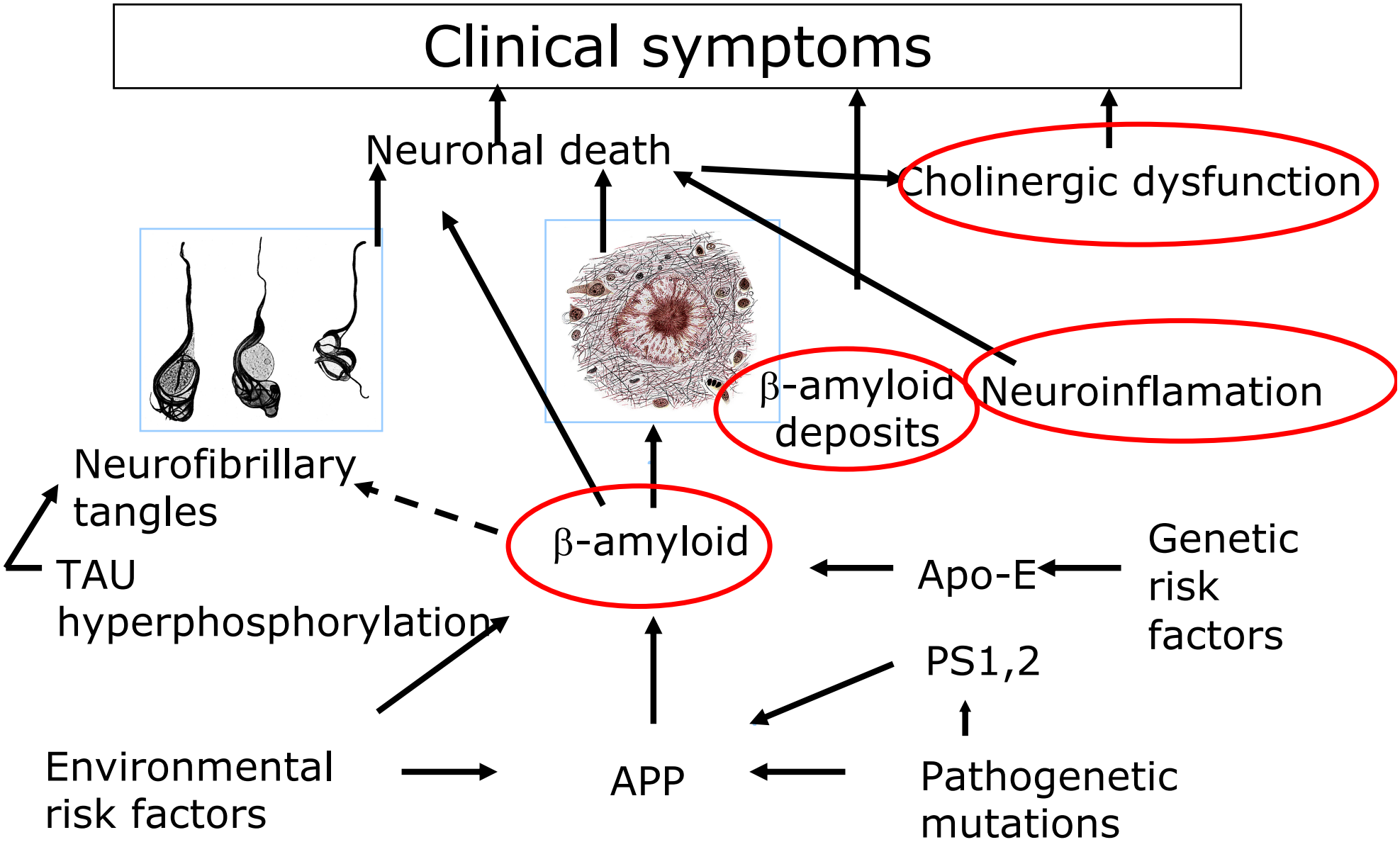


Alzheimer Diseases

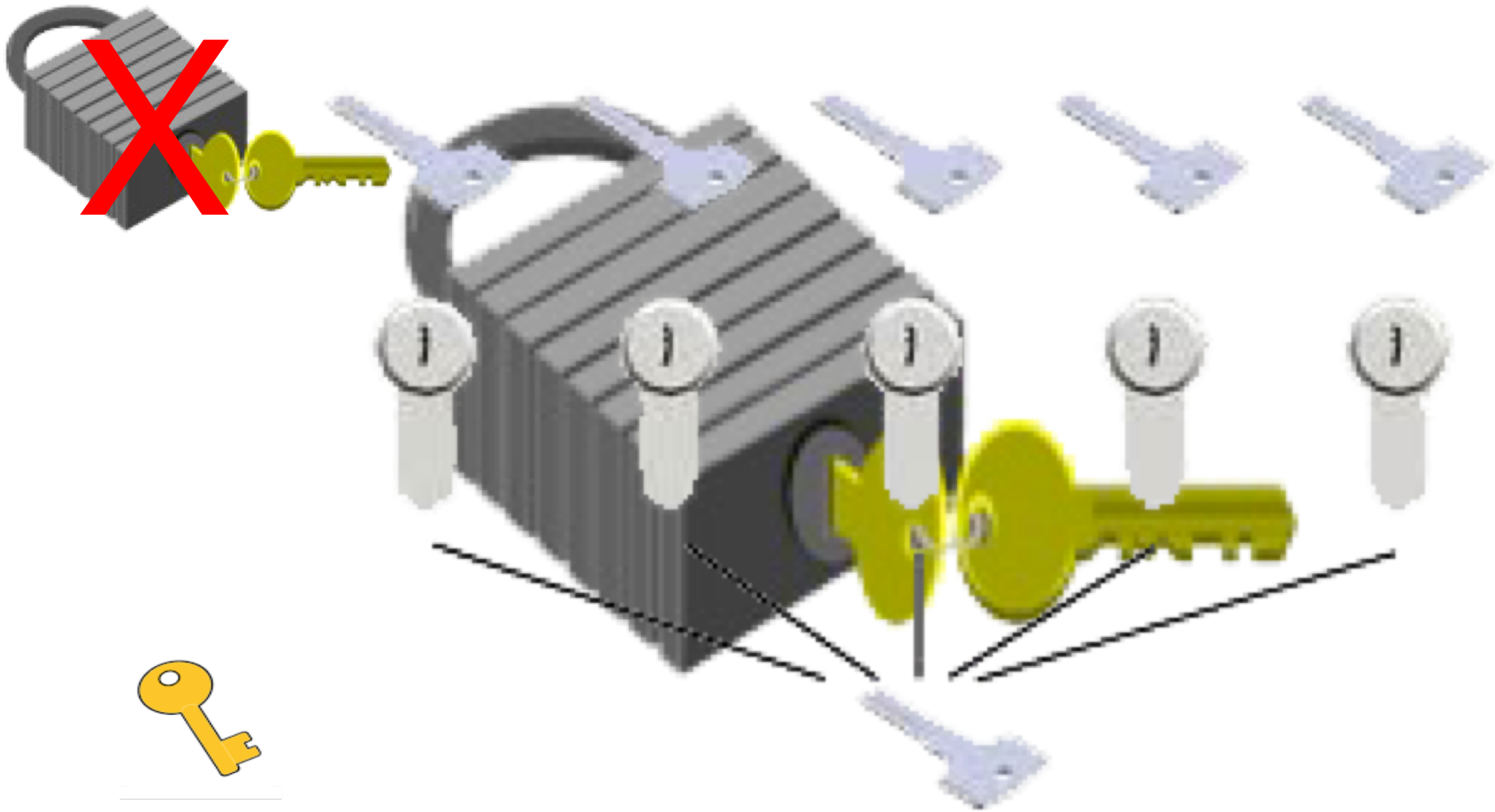
Alzheimer. Pathological cascade



Alzheimer. Pathological cascade



Multitarget ligands



Master key

Multitarget Drug

MULTITARGET DRUGS

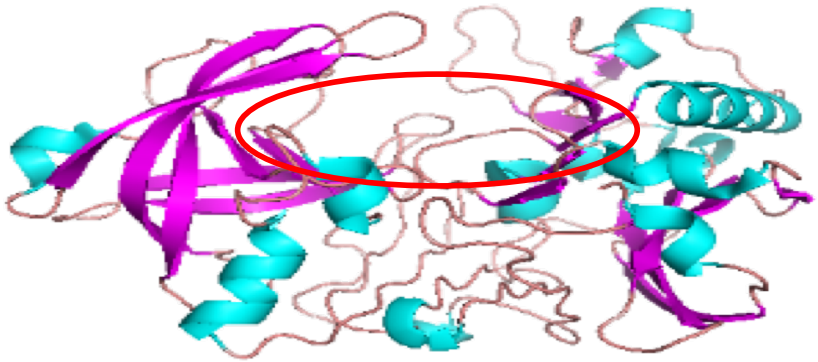
Objectives

Biological evaluation

	Compounds	BuChE (IC_{50} μM) (inh. Type)	BACE-1 (%Inh.)	Cannabinoid effect % inhibition contractile response ([10^{-6}/10^{-5}])
	WIN 55, 212-2		-	54.6/74.7 CB1/CB2 (A)
	PGN33	4.8 ± 0.3	-	74.7/86.4 CB2 (A)
BuChE BACE-1	NP145	6.4 (M)	53%	No Effect
	NP73	3.9 (C)	50%	No Effect
BuChE CB2	NP152	0.00026 (M)	11%	69.2/93.7 CB1/CB2 (A)
	NP101	0.62 (M)	18%	80.5/87.2 CB1/CB2 (A)
	NP91	0.39 (M)	11%	30.7/56.8 CB2 (PA)
	NP43	0.23 (M)	33%	56.3/80.8 CB2 (A)
	NP129	0.8 (M)	34%	54.7/80.5 CB2 (A)
	NP148	0.0025 (M)	38%	74.4/94.7 CB2 (A)
BACE-1 CB2	NP137	$>10^{4}$ (M)	60%	88.5/96.0 CB2 (A)
BuChE	NP124	0,00007 (M)	55%	31.5/55.9 CB1/CB2 (PA)
BACE-1 CB2	NP120	0.08 (M)	45%	89.3/96.6 CB2 (A)

M. Mixed-type; C. Competitive; A. Agonist; PA. Partial agonist

Binding site

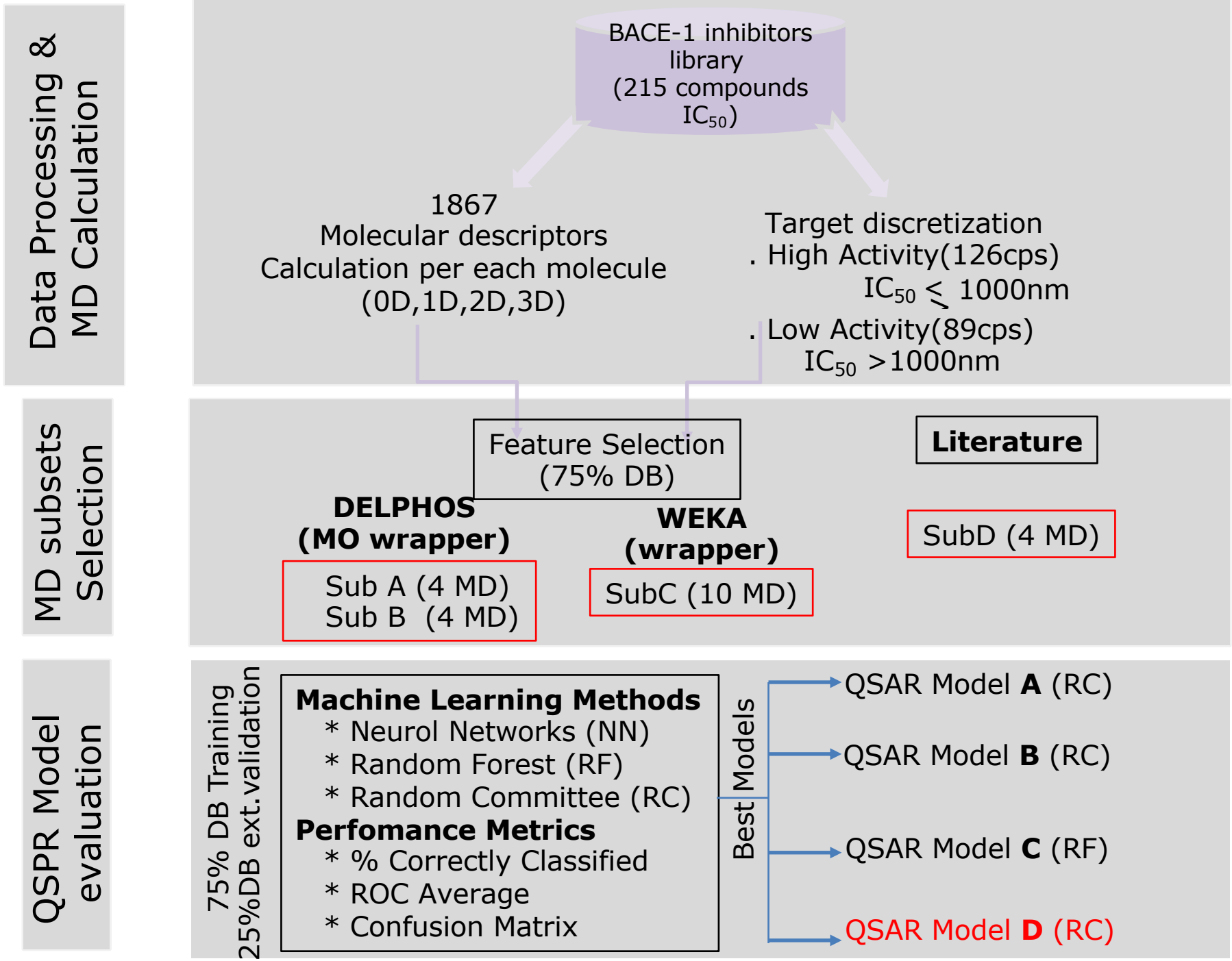


BACE-1

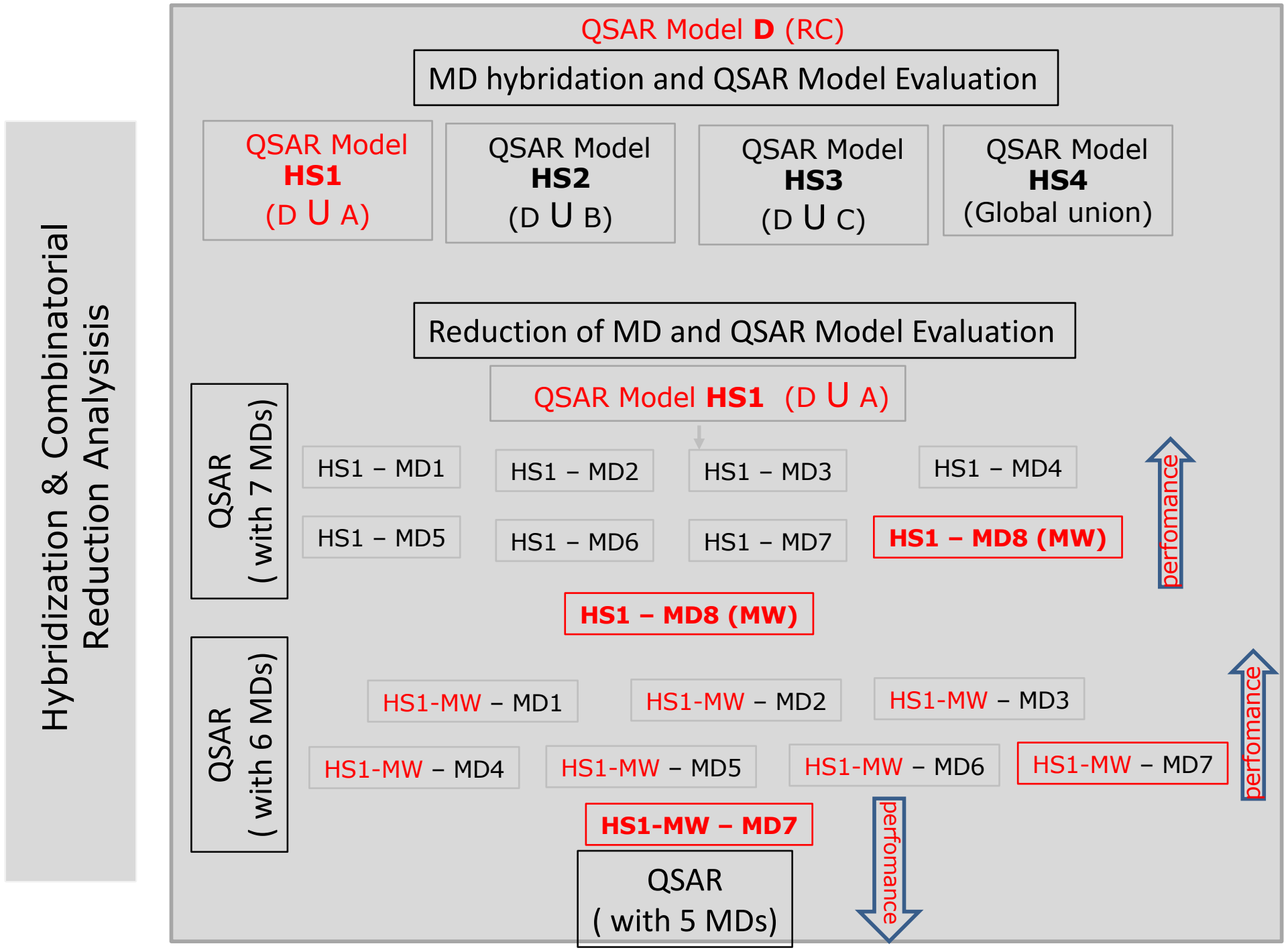
To develop a QSAR model to predict BACE-1 inhibitors

I. ponzoni *et al*. QSAR Classification Models for Predicting the Activity of Inhibitors of B-Secretase (BACE1) Associated with Alzheimer´s Disease. *Scientific Report*, **2019**, 9:9102

Protocol


Data Processing & MD Calculation
BACE-1 inhibitors library (215 compounds IC_{50})
1867 Molecular descriptors Calculation per each molecule (0D,1D,2D,3D)
Target discretization
. High Activity(126cps) $IC_{50} \leq 1000nm$
. Low Activity(89cps) $IC_{50} > 1000nm$
MD subsets Selection
Feature Selection (75% DB)
Literature
DELPHOS (MO wrapper)
Sub A (4 MD)
Sub B (4 MD)
WEKA (wrapper)
SubC (10 MD)
SubD (4 MD)
QSPR Model evaluation
75% DB Training 25%DB ext.validation
Machine Learning Methods
* Neurol Networks (NN)
* Random Forest (RF)
* Random Committee (RC)
Perfomance Metrics
* % Correctly Classified
* ROC Average
* Confusion Matrix
Best Models
QSAR Model A (RC)
QSAR Model B (RC)
QSAR Model C (RF)
QSAR Model D (RC)

Protocol


Hybridization & Combinatorial Reduction Analysisis
QSAR Model D (RC)
MD hybridation and QSAR Model Evaluation
QSAR Model HS1 (D U A)
QSAR Model HS2 (D U B)
QSAR Model HS3 (D U C)
QSAR Model HS4 (Global union)
Reduction of MD and QSAR Model Evaluation
QSAR Model HS1 (D U A)
QSAR (with 7 MDs)
HS1 – MD1
HS1 – MD2
HS1 – MD3
HS1 – MD4
HS1 – MD5
HS1 – MD6
HS1 – MD7
HS1 – MD8 (MW)
perfomance
HS1 – MD8 (MW)
QSAR (with 6 MDs)
HS1-MW – MD1
HS1-MW – MD2
HS1-MW – MD3
HS1-MW – MD4
HS1-MW – MD5
HS1-MW – MD6
HS1-MW – MD7
perfomance
HS1-MW – MD7
QSAR (with 5 MDs)
perfomance

Subset	Step	Cardinality	Method	%CC	ROC	Confusion Matrix		
						High	*Low*	
HS1 - MW	1	7	RF	85	0.85	28	3	*High*
						5	16	*Low*
						High	***Low***	
HS1 - MW - RDF080m	***2***	***6***	***RF***	***85***	***0.88***	***30***	***1***	***High***
						7	***14***	***Low***
						High	*Low*	
HS1 - MW - –N-069	3	5	RF	83	0.89	29	2	*High*
						7	14	*Low*

Table 6. Performances during external validation of the best QSAR classifiers inferred for HS1 reduced subsets in each step. The final model has 6 molecular descriptors, an 85% of cases correctly classified and a ROC curve of 0.88.

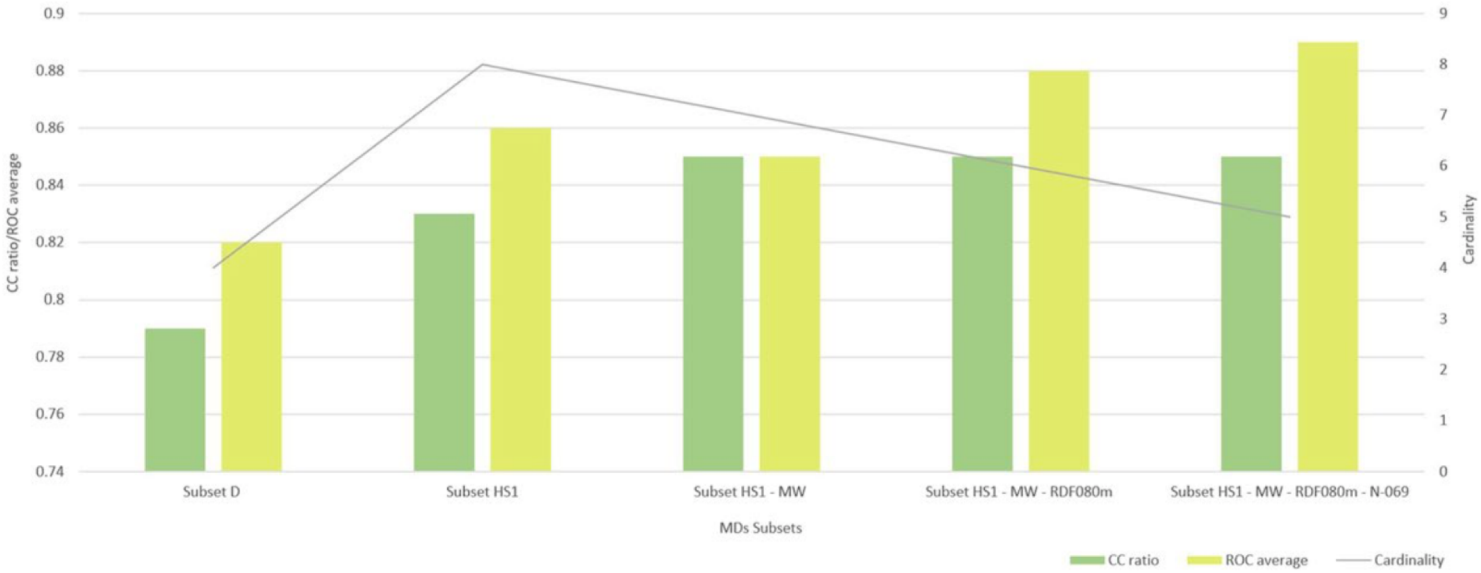


Figure 3. Performance during external validation of the best QSAR model achieved in each experimental step.

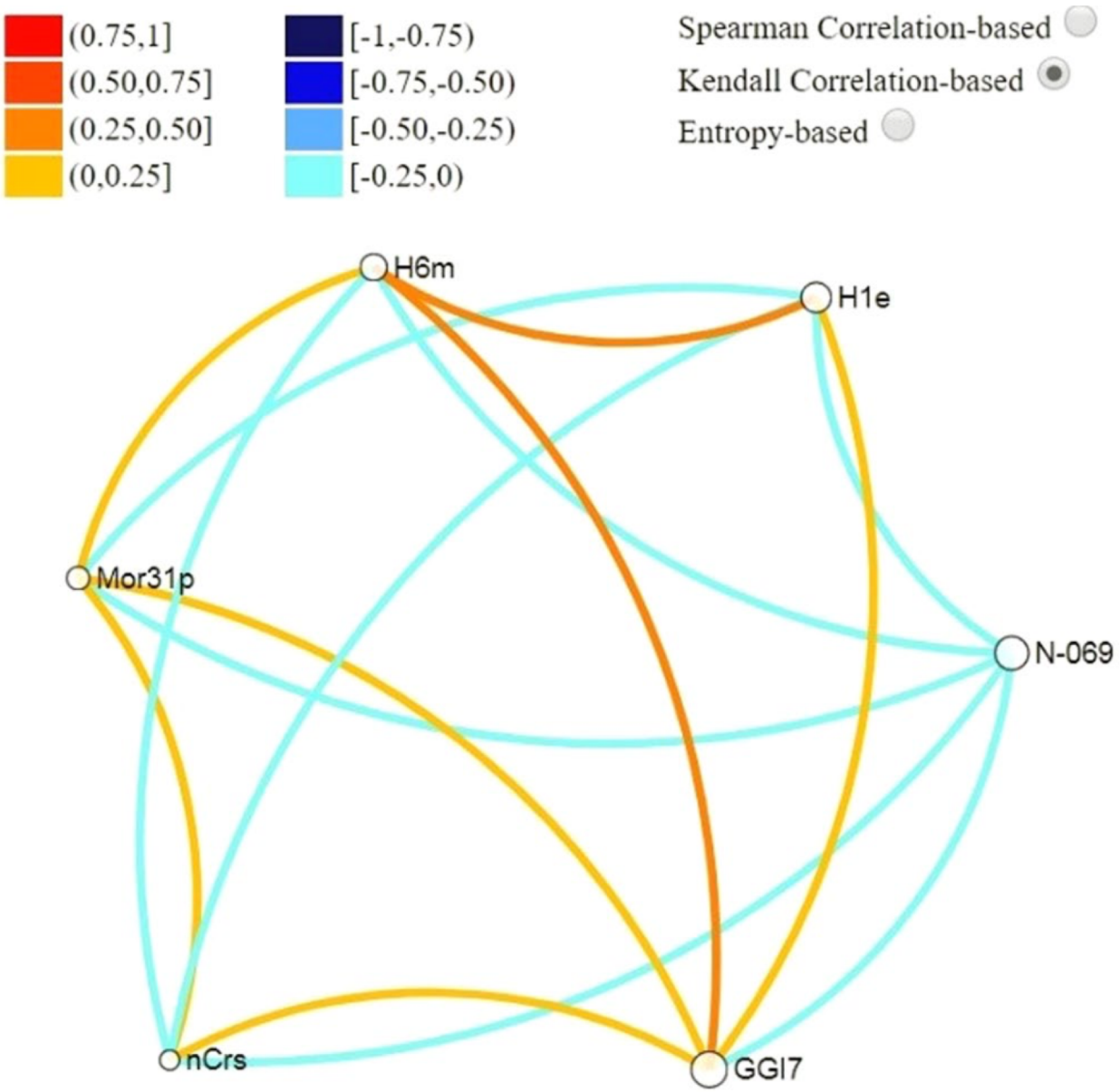
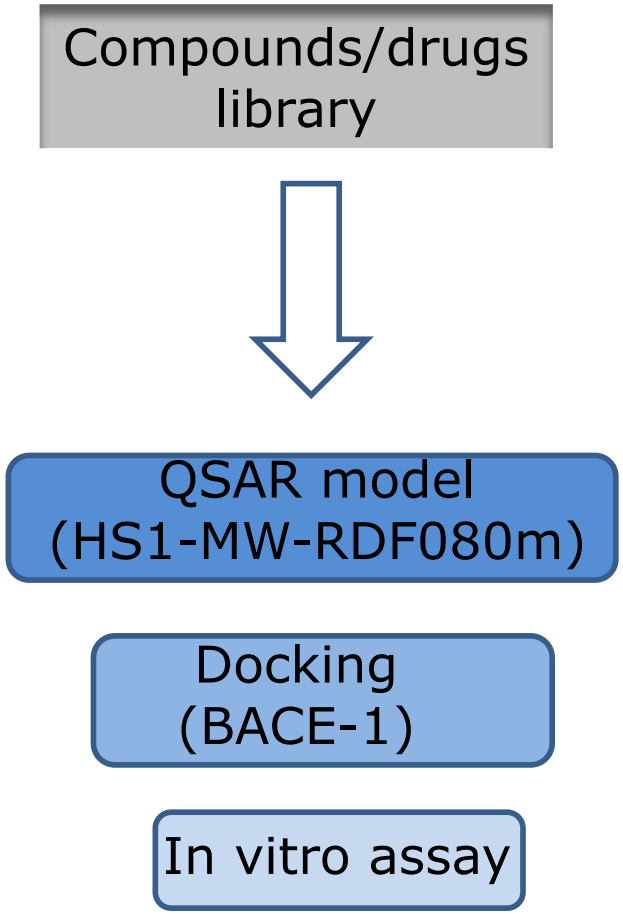


Figure 4. Kendall correlation among descriptors of the best model.

Results


Compounds/drugs library
QSAR model (HS1-MW-RDF080m)
Docking (BACE-1)
In vitro assay

Altenea® biotech

SOLUCIONES SOBRE NOSOTROS CONTACTO

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Ciencia, Inteligencia Artificial e Innovación para crear un mundo inteligente

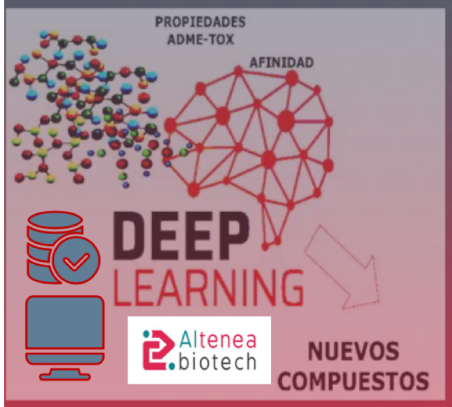
Aplica los beneficios de la IA en tu sector para generar el máximo valor de transformación

Descubre Aitenea

Altenea biotech

THE SOLUTION

A prediction system developed by Altenea biotech, based on Artificial Intelligence techniques that improves the identification of pharmacological objectives and the design of new drugs.



- Lower economic and time costs at different preclinical stages in drug development
- Decrease the failure ratio
- Decrease animal experimentation

SAVINGS

Candidate development | **Preclinical Phase**

40%-50% time
$ 26 billions/year

Clinical Trials

50%-60% time
$ 28 billions/year

TechEmergence Report 2019

PLATFORM USE PROCESS DESCRIPTION

STEP 1

Researchers are developing new drugs that want to predict what their "drug-like" properties may be

STEP 2

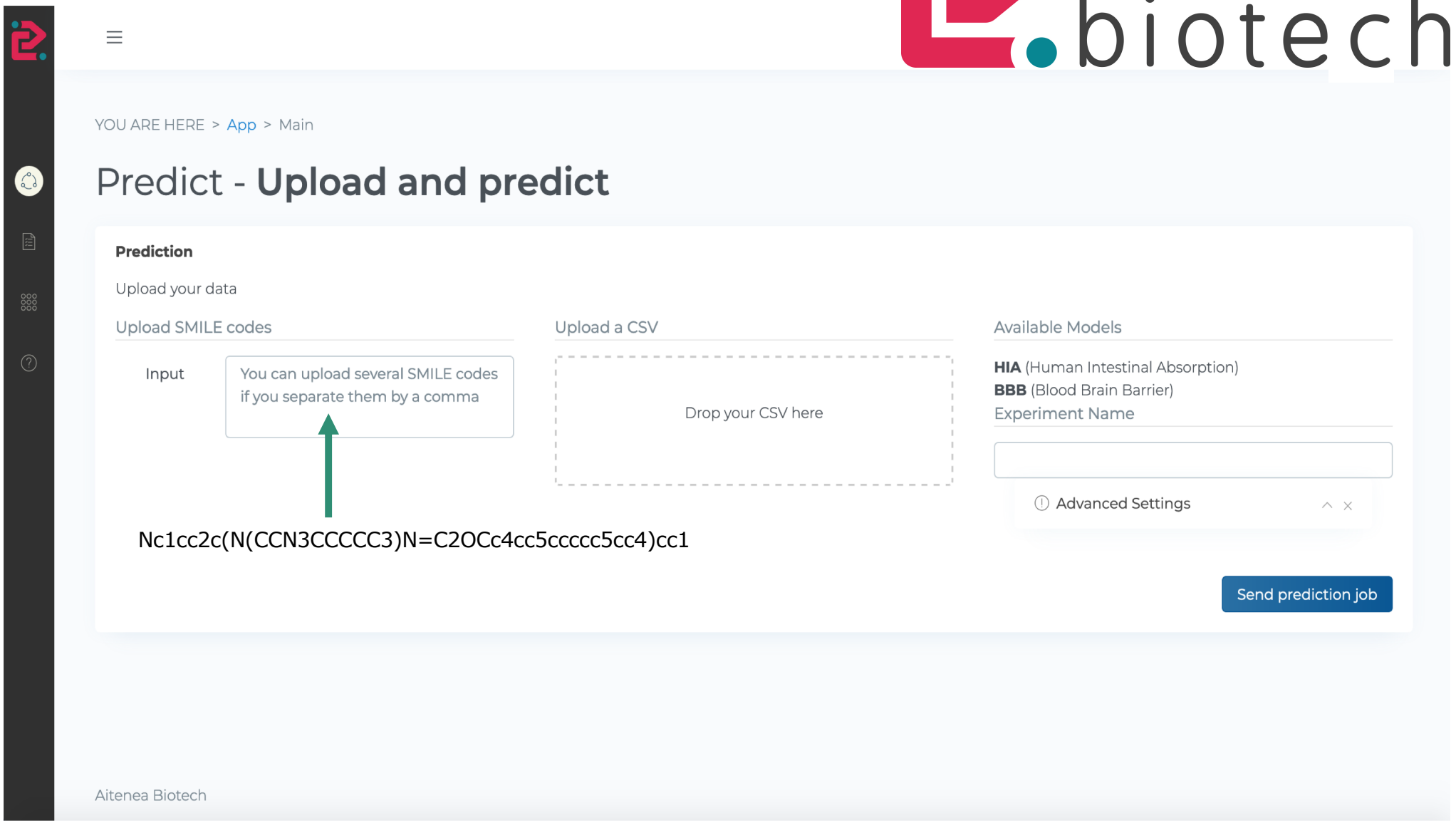
The user has access to the online platform. Easily and intuitively climbs molecule structures and decides which properties you want to predict

STEP 3

Using predictive models located in cloud systems, your predictions are calculated

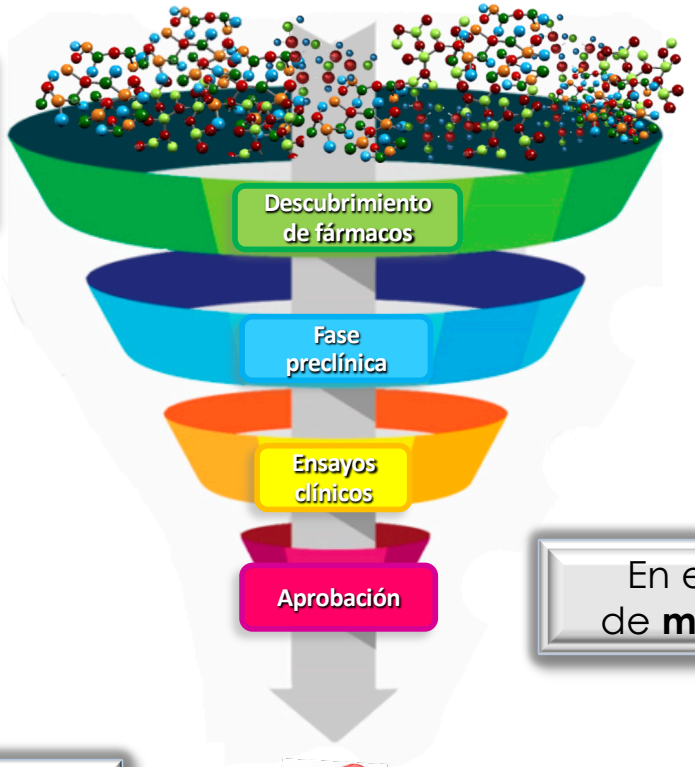
STEP 4

A report is developed automatically, explaining the results of the prediction


YOU ARE HERE > App > Main
Predict - Upload and predict
Prediction
Upload your data
Upload SMILE codes
Input
You can upload several SMILE codes if you separate them by a comma
Upload a CSV
Drop your CSV here
Available Models
HIA (Human Intestinal Absorption)
BBB (Blood Brain Barrier)
Experiment Name
Advanced Settings
Nc1cc2c(N(CCN3CCCCC3)N=C2OCc4cc5ccccc5cc4)cc1
Send prediction job
Aitenea Biotech

IA en .....

Identificación
y optimización multi-paramétrica
de nuevos **fármacos**



En el desarrollo
de **medicamentos**

Inteligencia Artificial y Big Data
análisis de datos

Determinación
de **dosis**