

Ligand Target Prediction & Promises & Pitfalls of Machine Learning in Chemistry

Special Interest Group Meet #1

Manas Mahale | Mon, 7 Aug 2023 | 5:30 PM | Room 016

About this talk

Reference

CXCR4 expression is elevated in TNBC patient derived samples and Z-guggulsterone abrogates tumor progression by targeting CXCL12/CXCR4 signaling axis in preclinical breast cancer model.

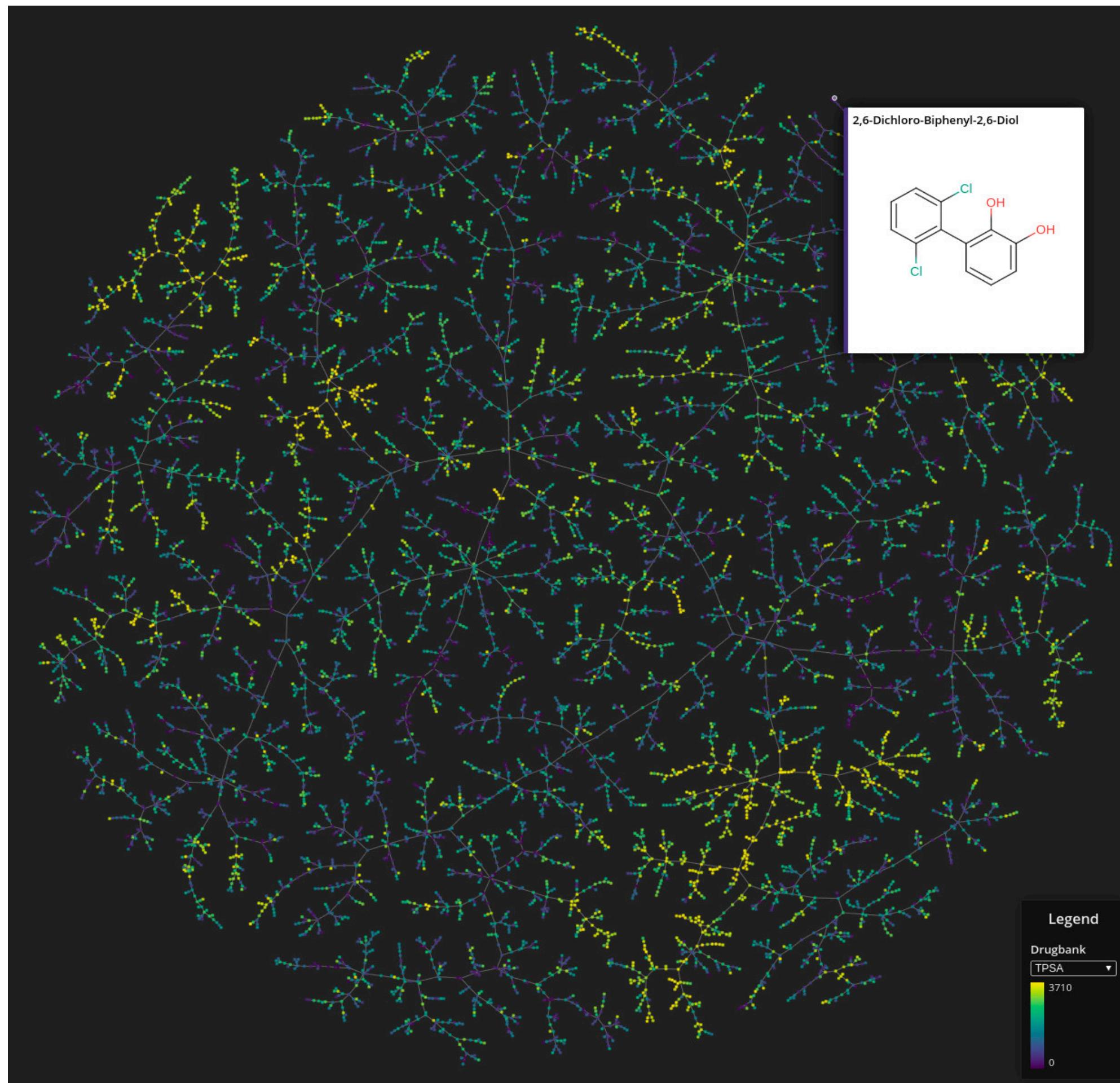
Gupta, N., Mohan, C. D., Shanmugam, M. K., Jung, Y. Y., Chinnathambi, A., Alharbi, S. A., Ashrafizadeh, M., *Mahale, M.*, Bender, A., Kumar, A. P., Putti, T. C., Rangappa, K. S., Zhang, X., Ahn, K. S., & Sethi, G. (2023). Environmental Research, 232, 116335.

<https://doi.org/10.1016/j.envres.2023.116335>

What is “Ligand-Target Prediction” ?

What is Ligand Target Prediction ?

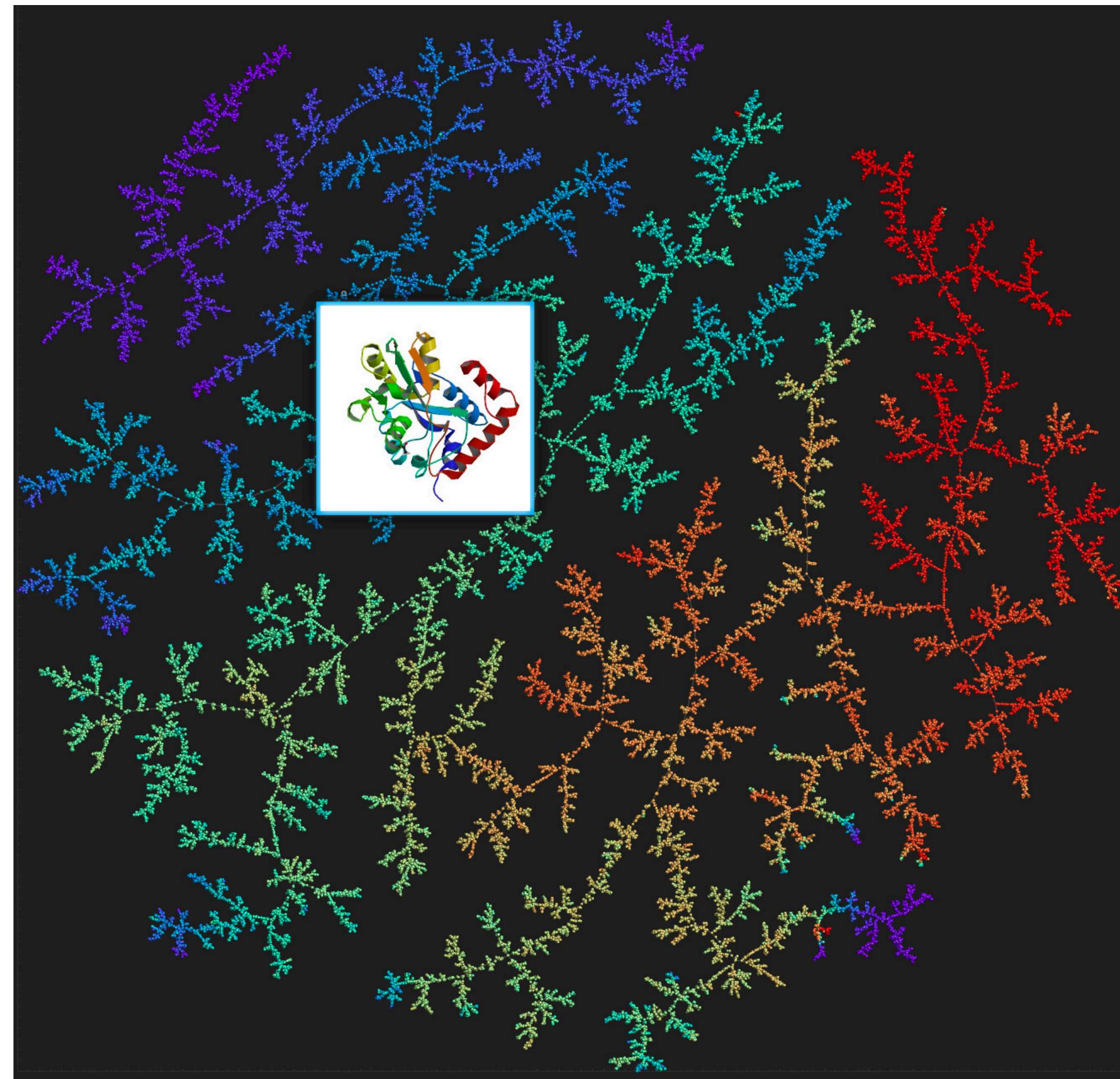
Nature of Ligand



TMAP of Drugbank (Probst et. al)

What is Ligand Target Prediction ?

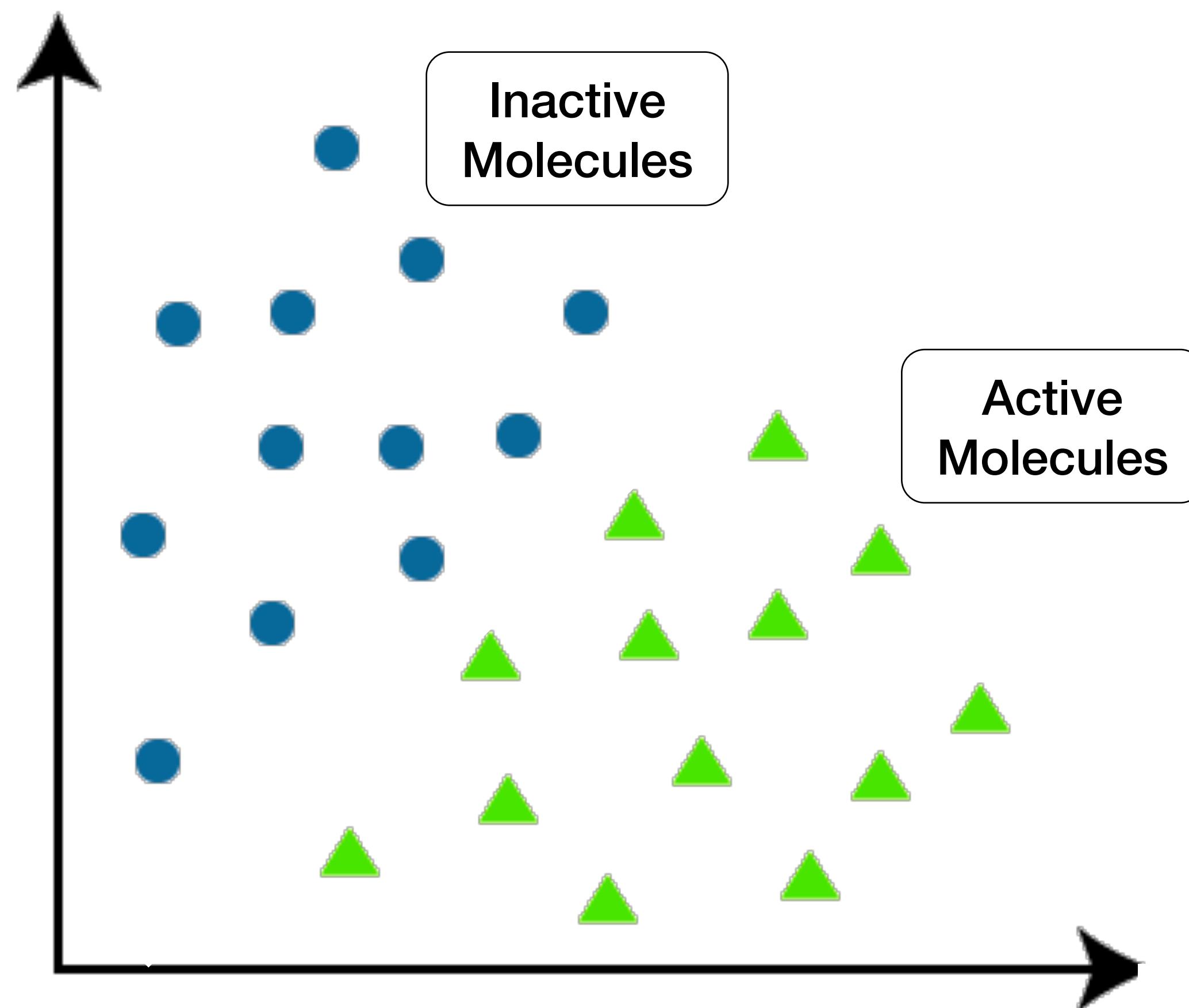
Nature of Target



TMAP visualization of Protein Data Bank (Probst et. al)

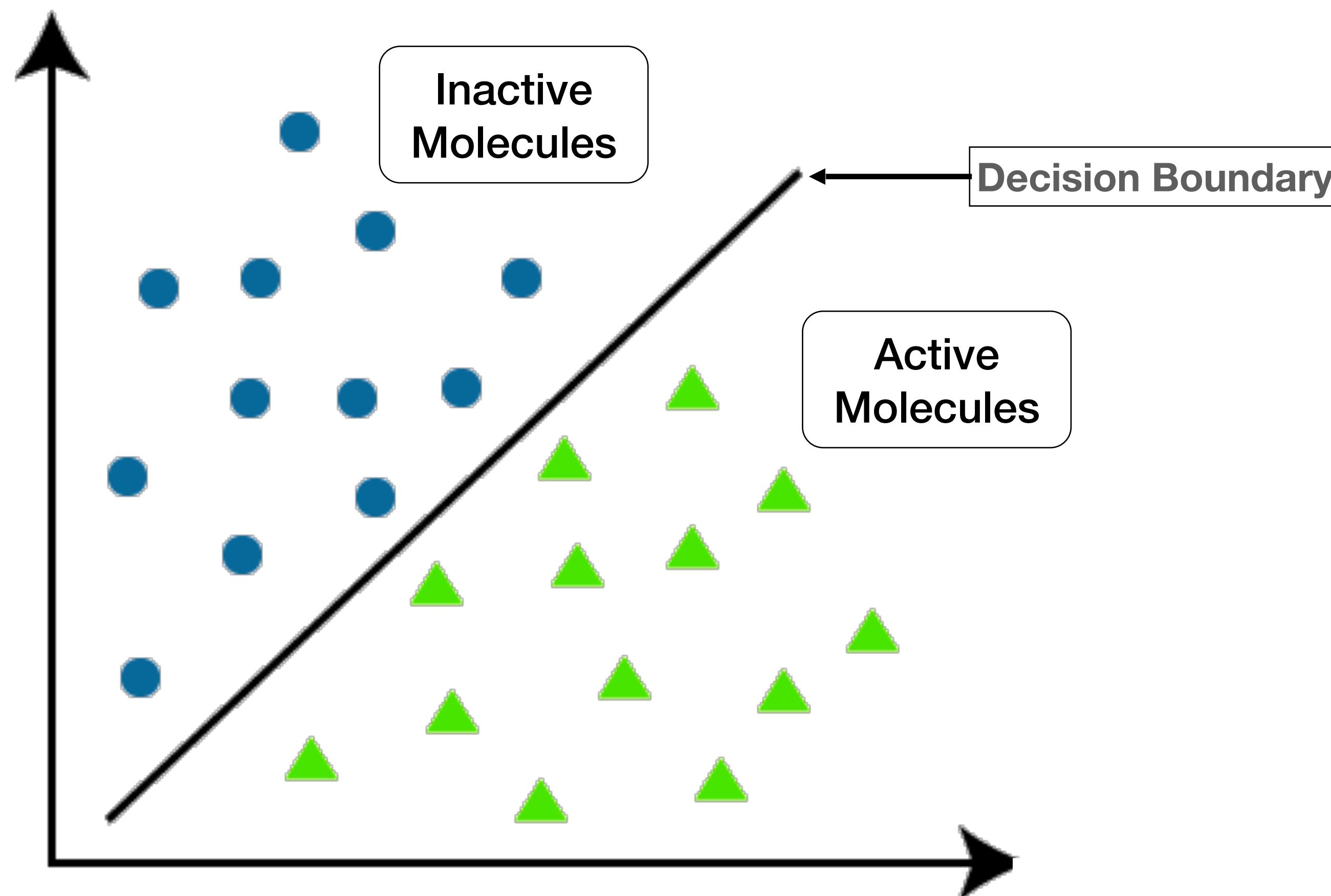
What is Ligand Target Prediction ?

Nature of Prediction



What is Ligand Target Prediction ?

Nature of Prediction



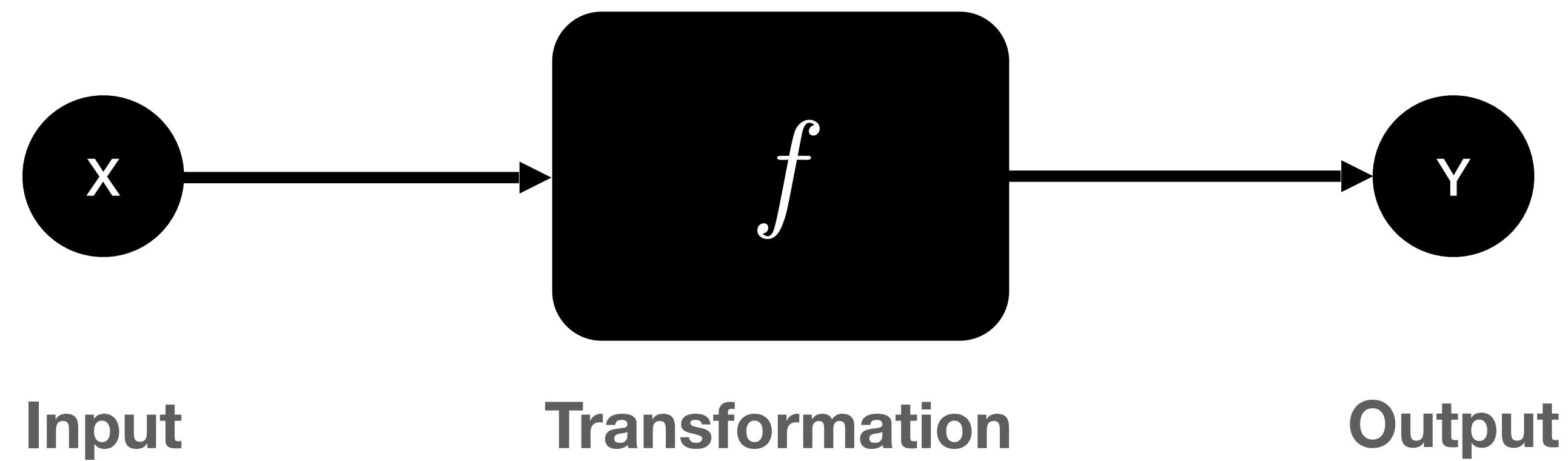
What is Ligand Target Prediction ?

What is a Machine Learning Model ?

$$Y = f(X)$$

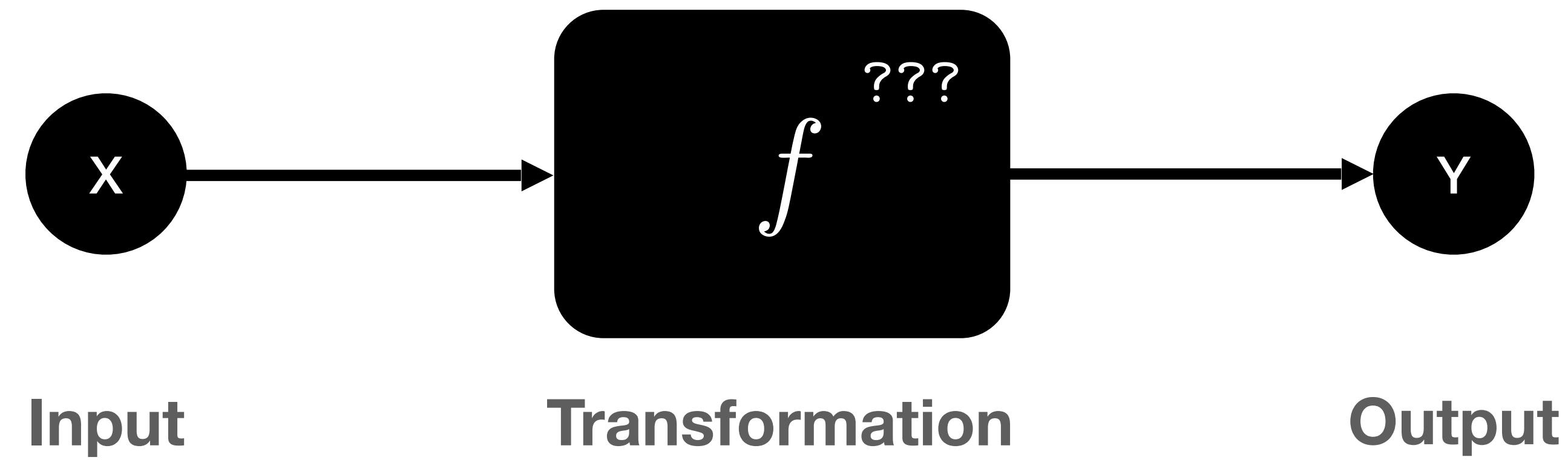
What is Ligand Target Prediction ?

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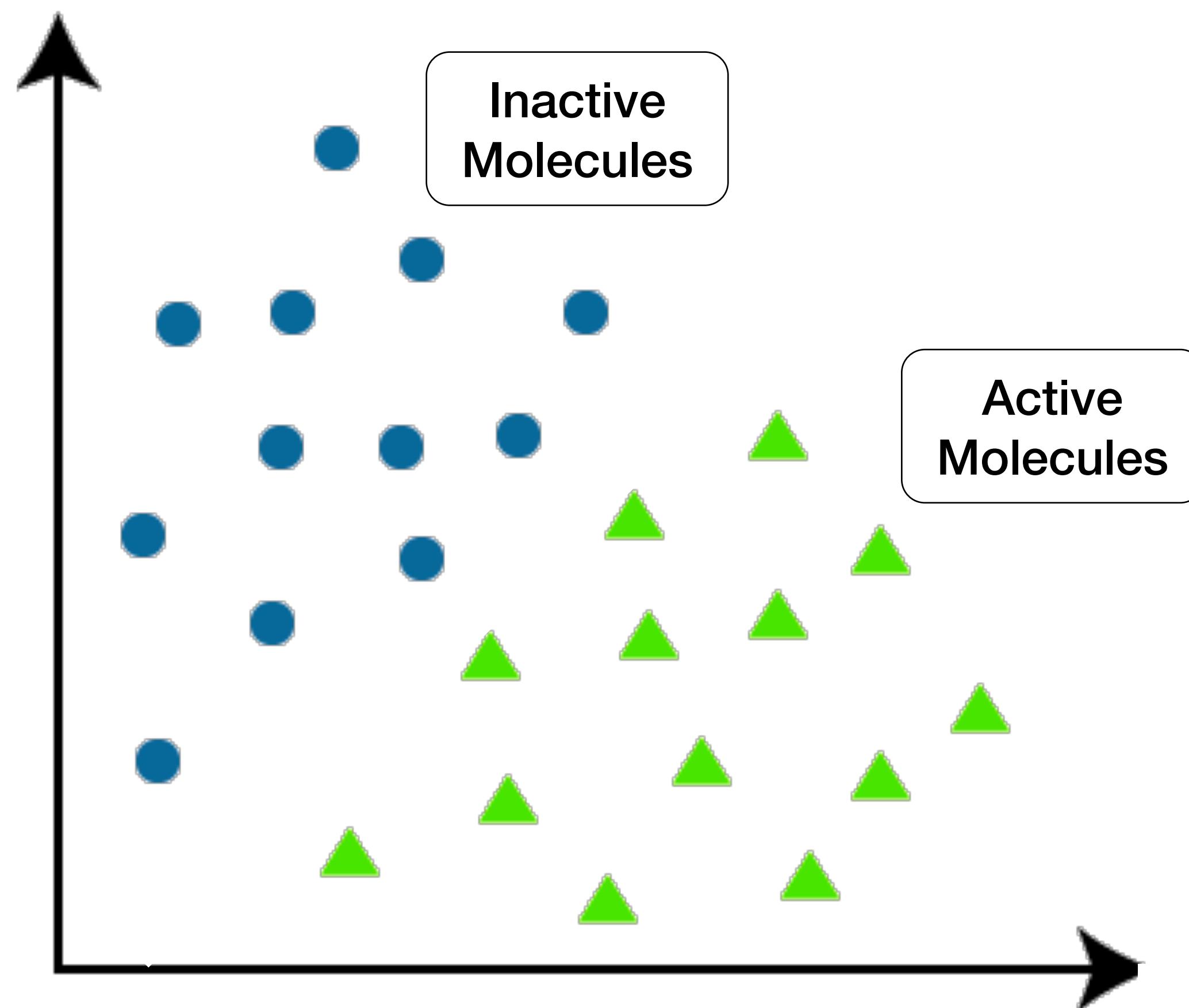
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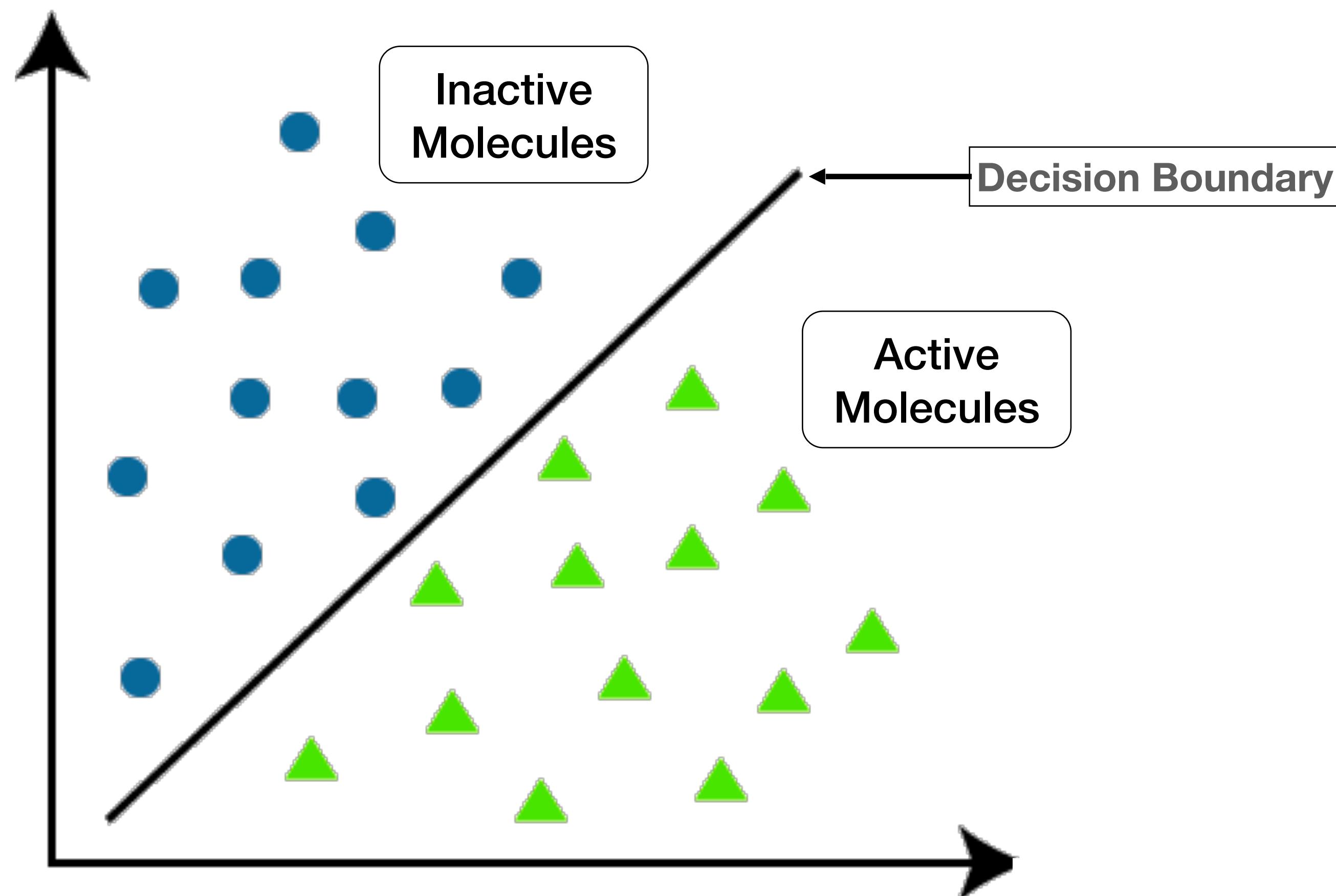
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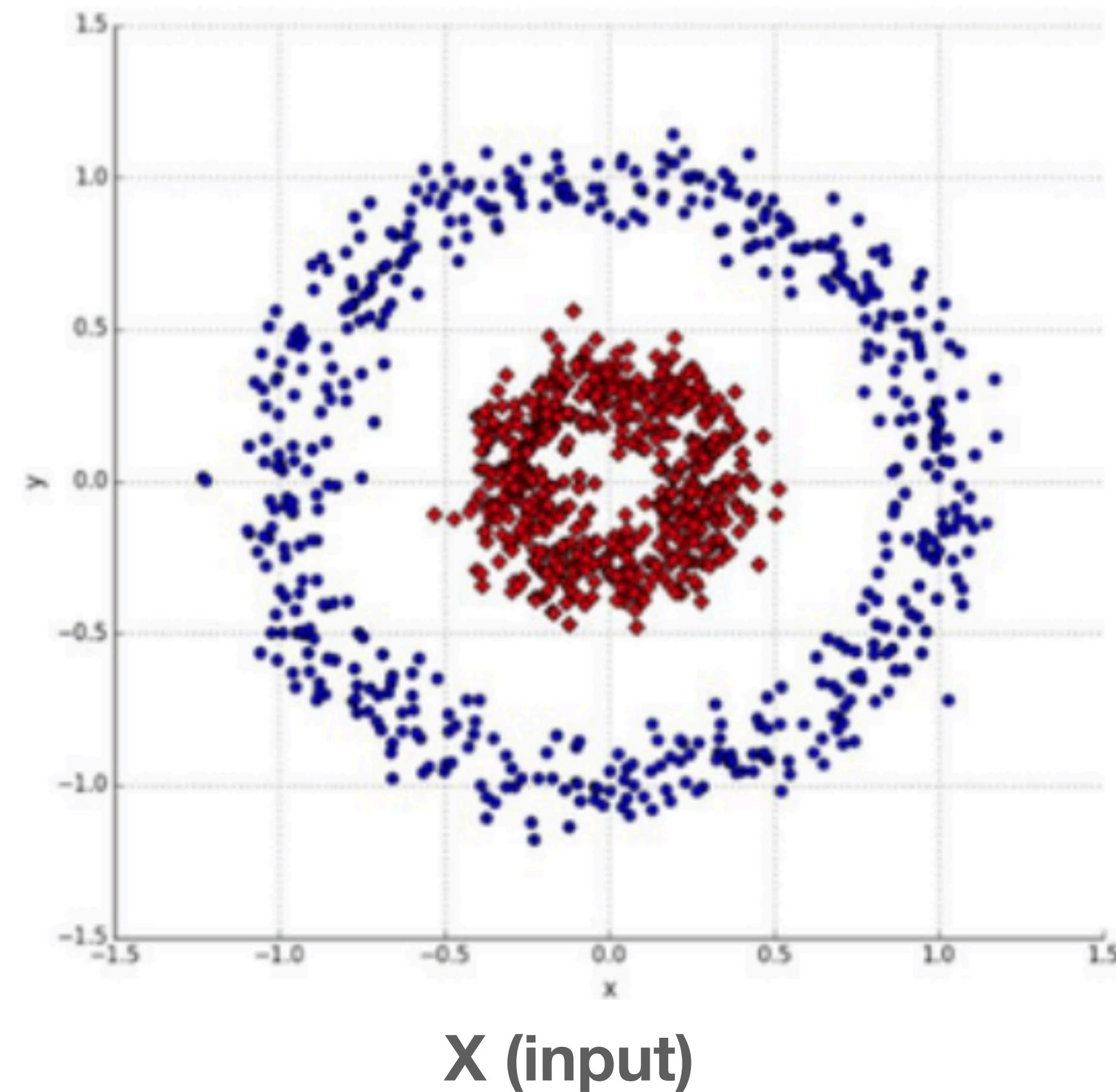
What is Ligand Target Prediction ?

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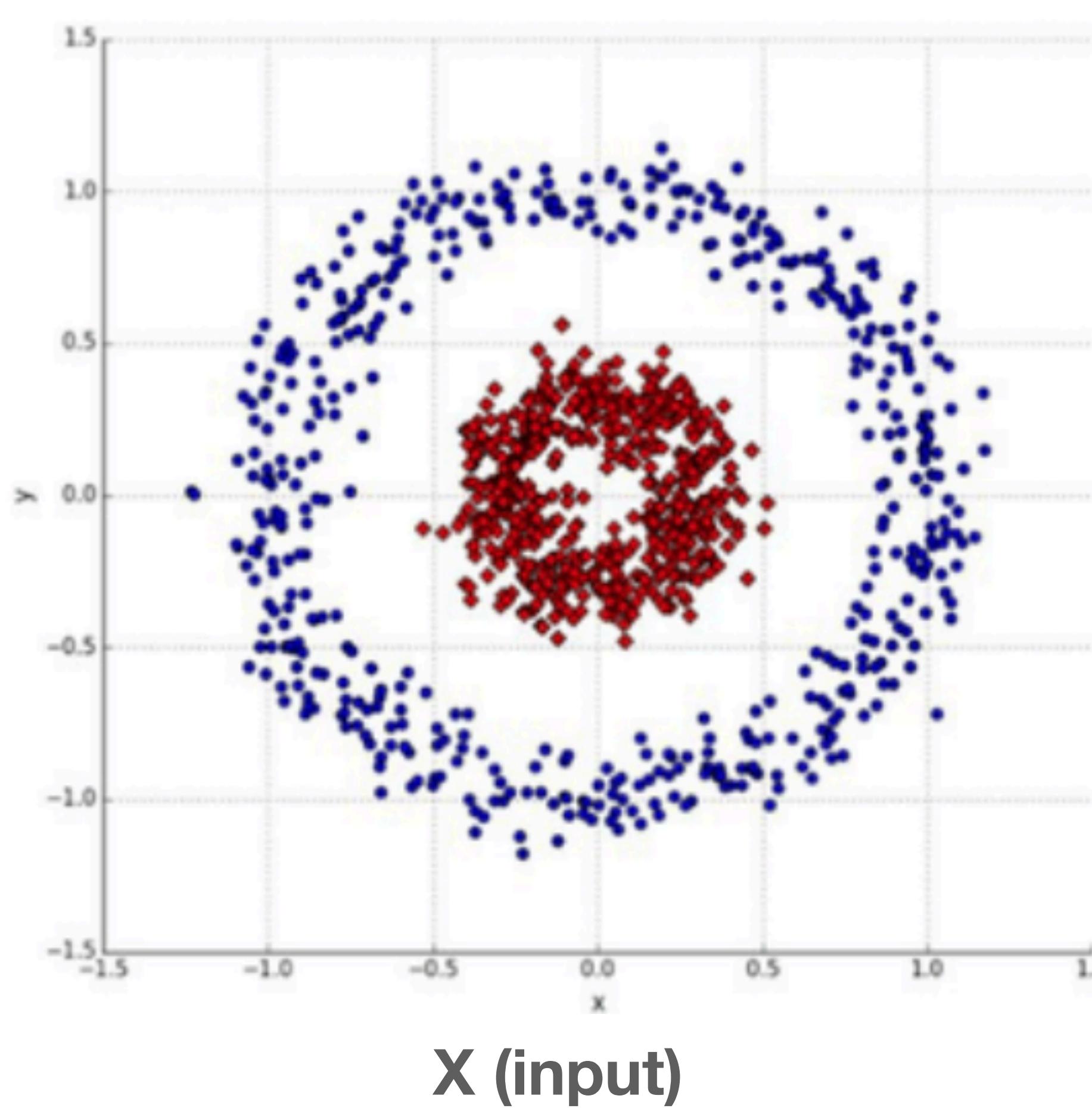
What is Ligand Target Prediction ?

What is a Machine Learning Model ?



What is Ligand Target Prediction ?

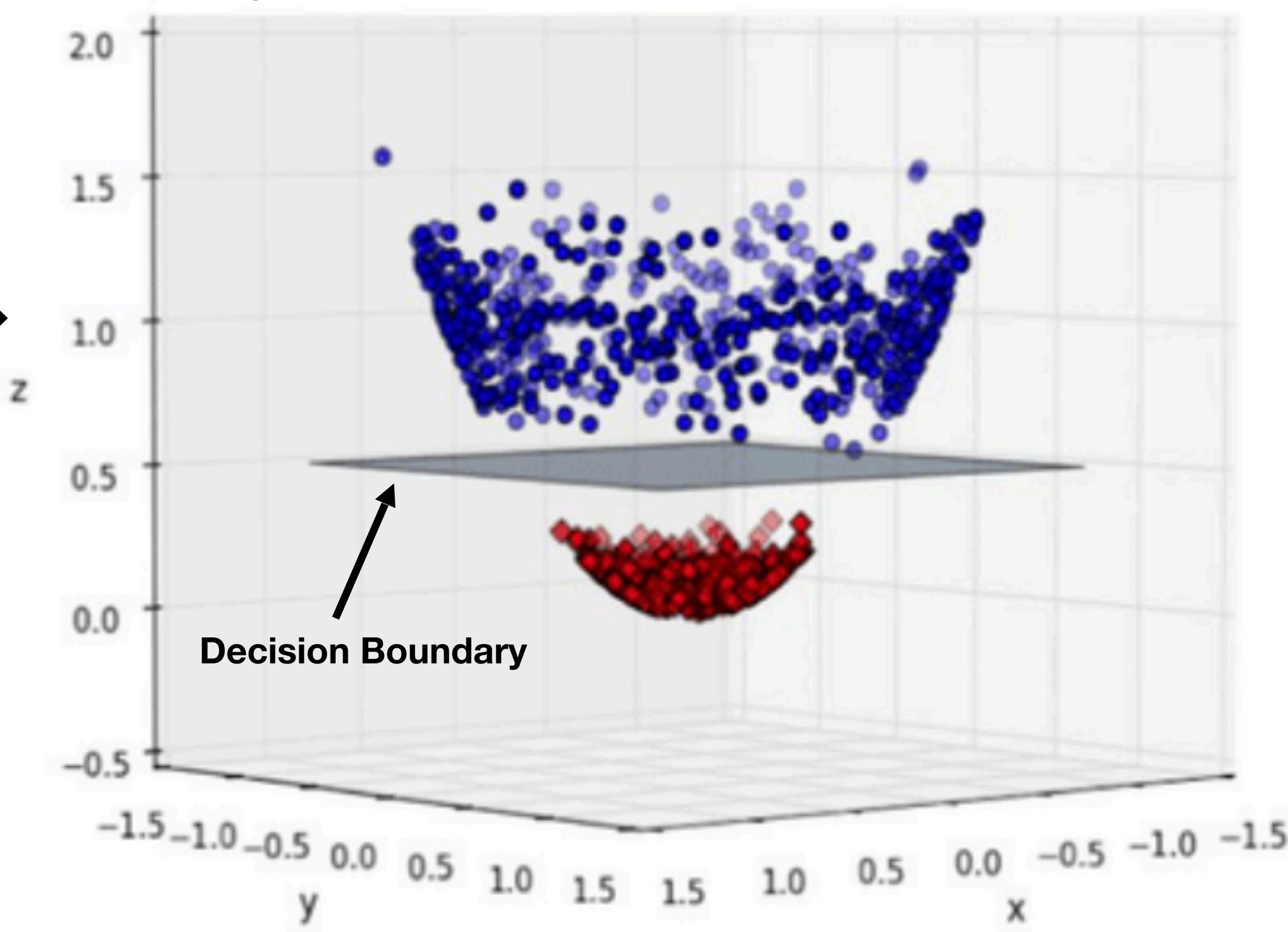
What is a Machine Learning Model ?



Transformation →

$$f = x^2 + y^2$$

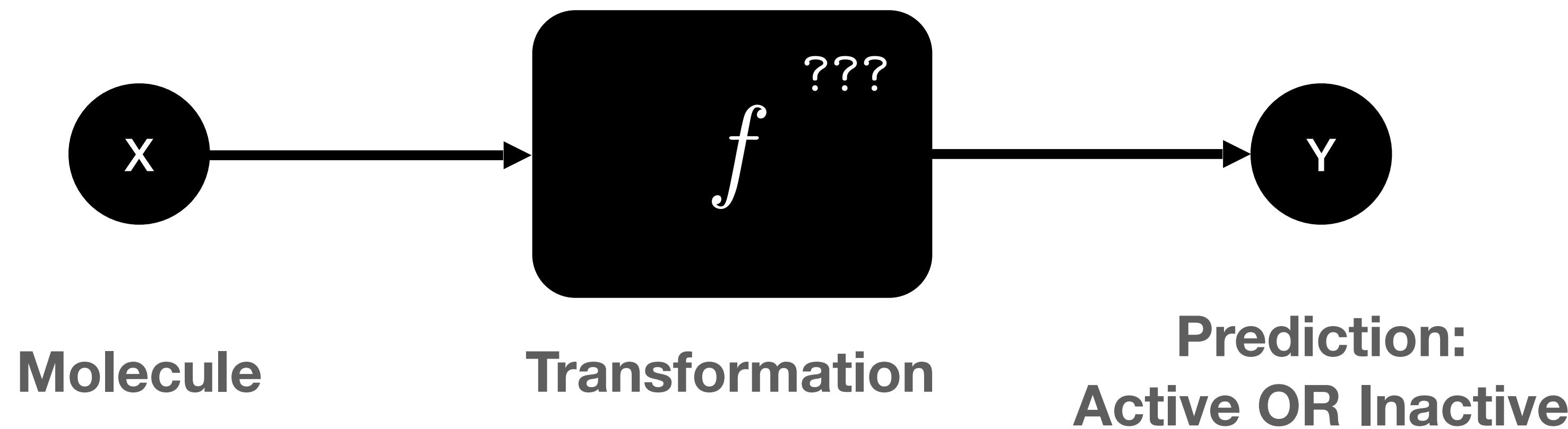
$$z = x^2 + y^2$$



**So, what is
“Ligand-Target Prediction” ?**

What is Ligand Target Prediction ?

What is a Machine Learning Model ?

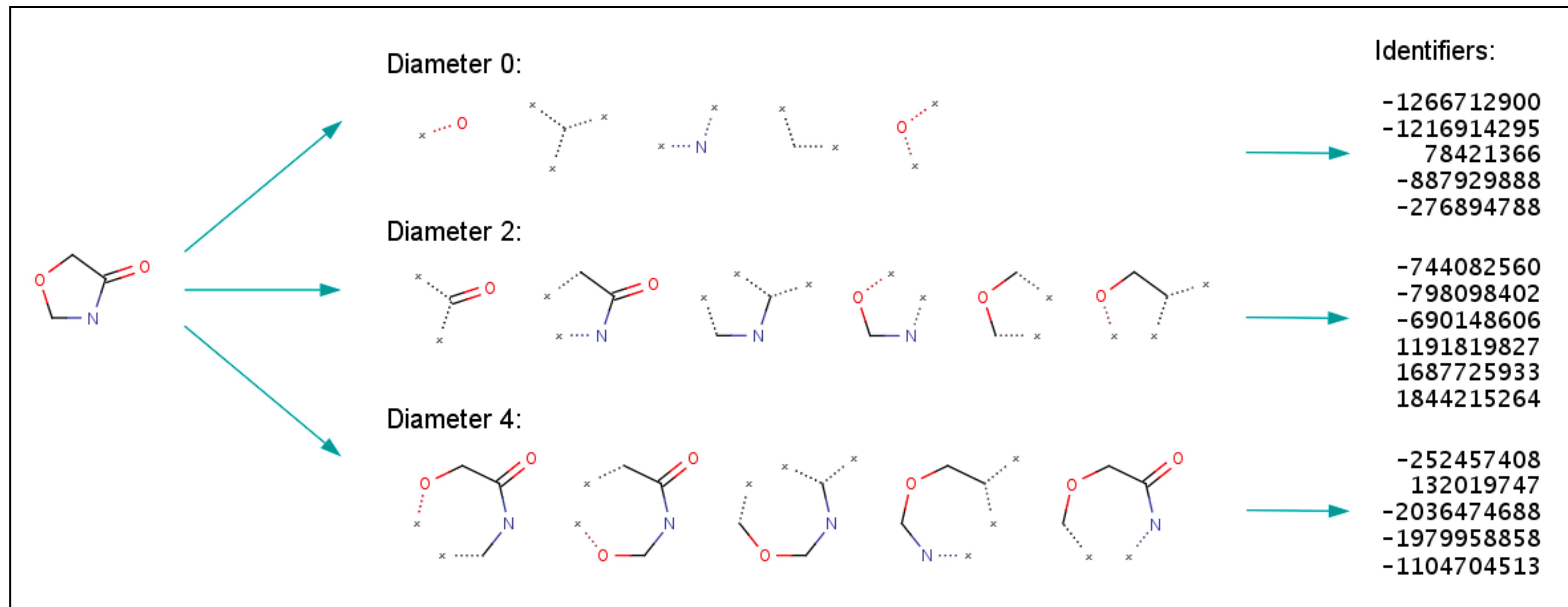


How is Chemistry represented *Computationally*?

Representing Ligand

Ligand Representation

Extended Circular Fingerprints



Rogers, David, and Mathew Hahn. "Extended-Connectivity Fingerprints." *Journal of Chemical Information and Modeling*, vol. 50, no. 5, May 2010, pp. 742–54

<https://doi.org/10.1021/ci100050t>

Representing Target

Target Representation

Why we don't represent Targets

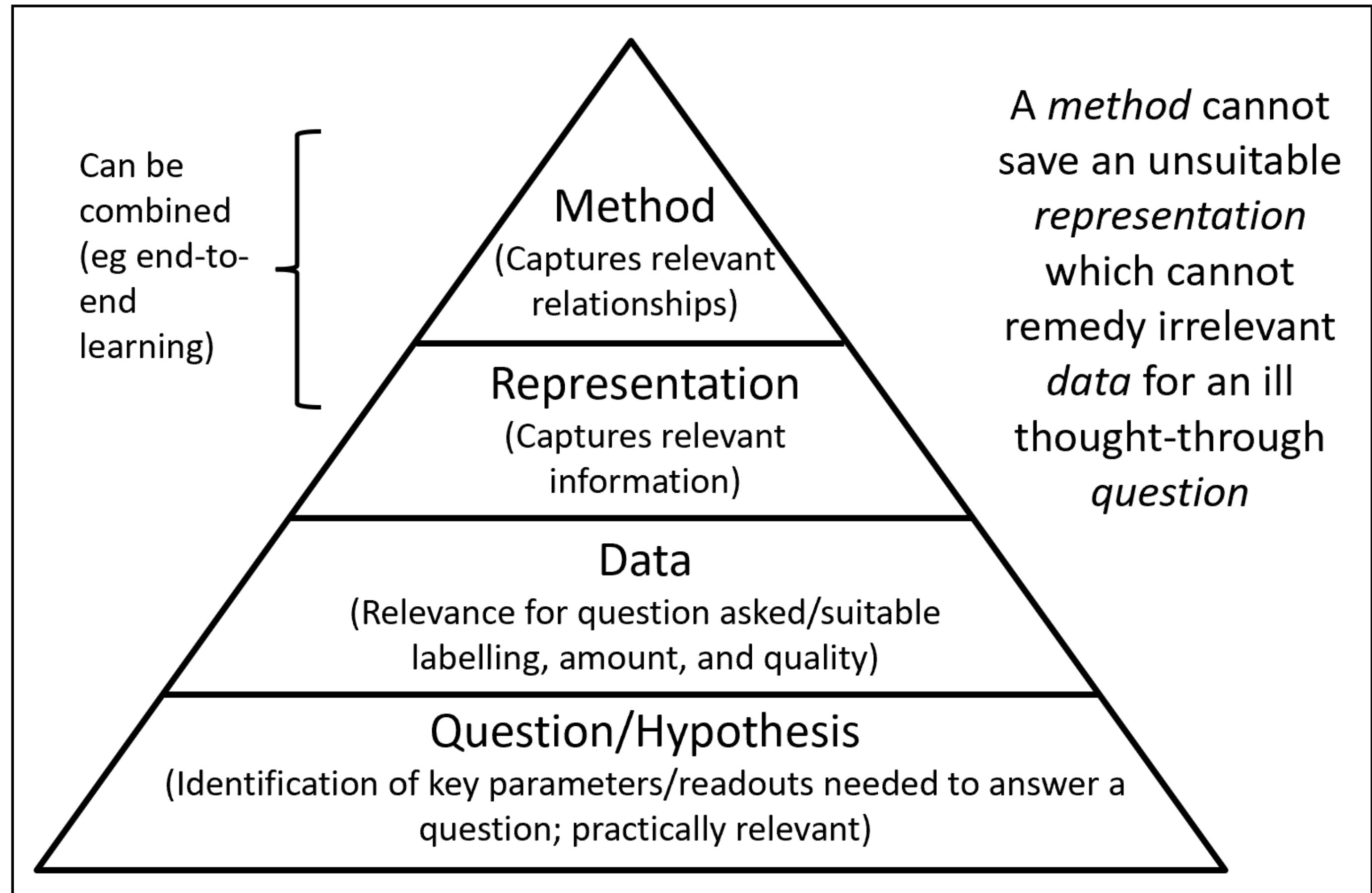
- Data Scarcity (Sparse public data and Expensive privately curated data)
- All other things being equal — we don't care about binding mode, up-or-downstream effects of binding or mechanism of binding
- Computationally Expensive

Machine Learning – Pitfalls

Machine Learning

Pitfalls

- **Data**
 - **Data Quality**
 - **Data Quantity**
 - **Data Splits**
 - **Coverage**

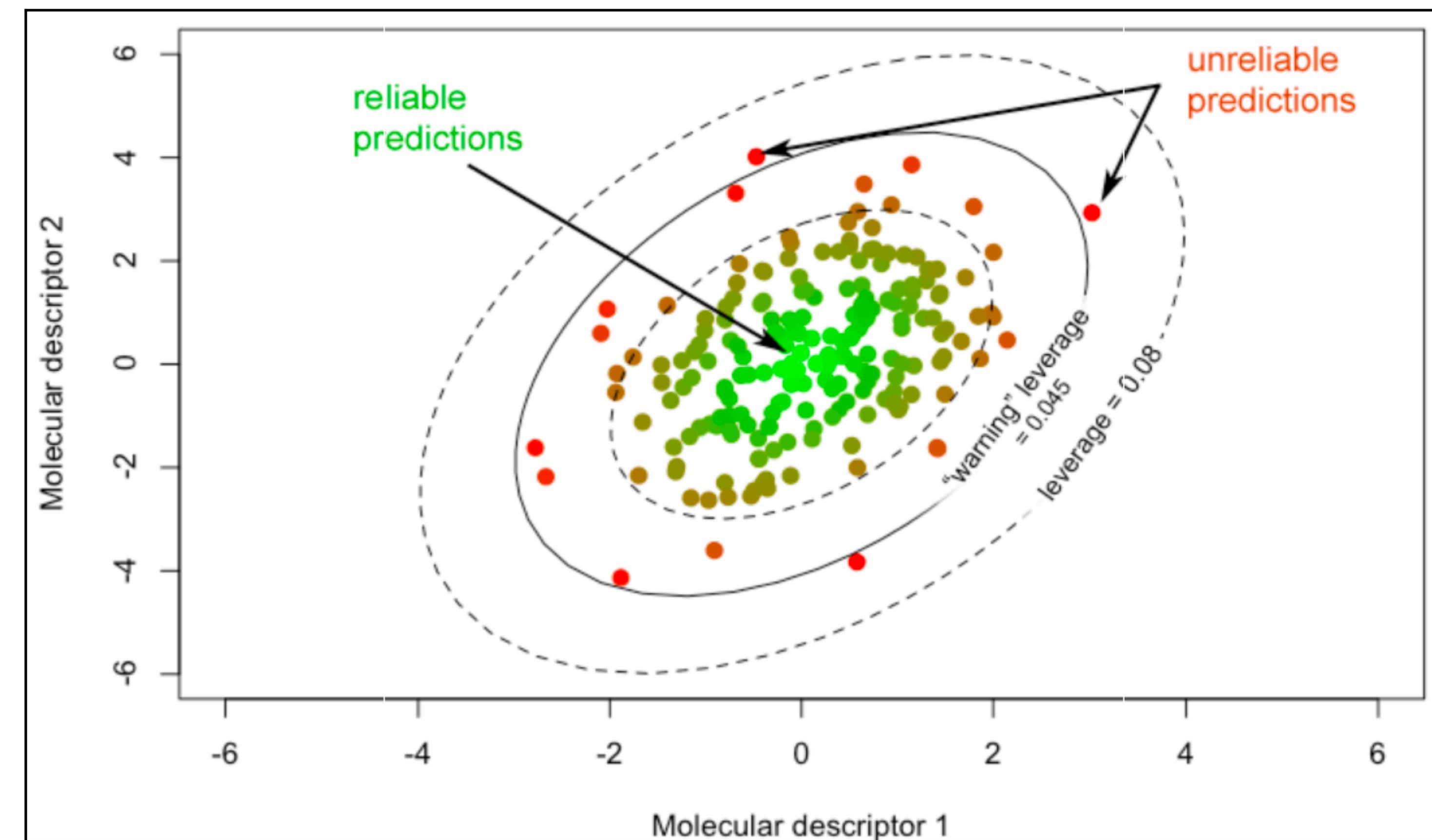


Data that is based on a suitable hypothesis will be of considerable more practical utility than data that has been generated in a hypothesis-free manner.

Machine Learning

Pitfalls

- **Applicability Domain**



Reading Material

[1] How to Lie With Computational
Predictive Models in Drug Discovery ?

[2] Will Robotics, AI and Cloud
Computing In Chemical Synthesis Save
Drug Discovery? A Closer Look

Conclusion

What you should know

- **Triple-negative breast cancer** is a variant of breast cancer that *lacks* therapeutic targets such as ***Progesterone receptor***, ***Estrogen receptor***, and ***Human epidermal growth factor receptor-2*** which makes the targeted therapy ineffective in TNBC patients.
- **CXCR4** was found to be *highly expressed* in majority of breast cancer tissues and metastatic lymph nodes derived from TNBC patients.

Experimental Findings

Hypothesis

- **CXCR4** expression is positively correlated with breast cancer metastasis and poor prognosis of TNBC patients.
- **Hypothesis :** Suppression of CXCR4 expression could be a good strategy in the treatment of TNBC patients.

Experimental Findings

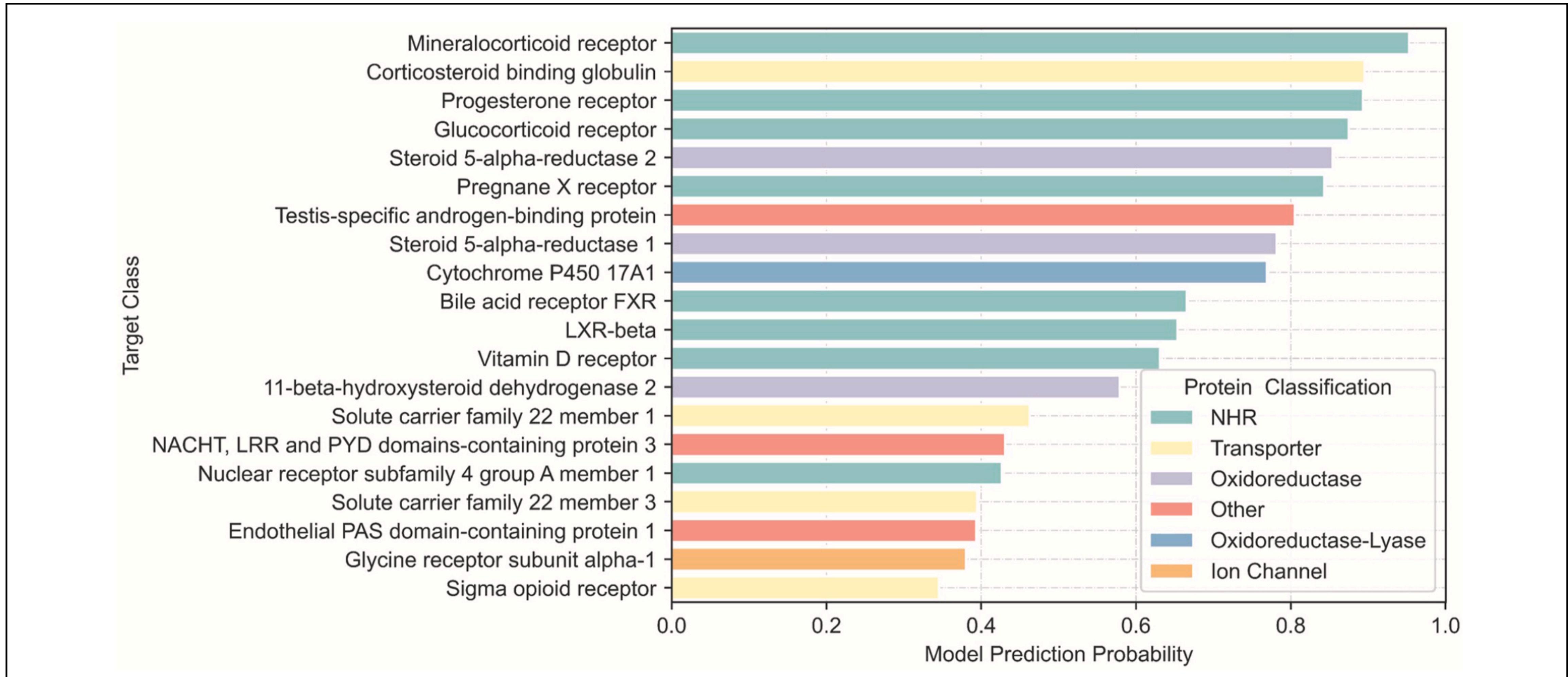
Key Results

- **CXCR4** is under the transcriptional control of **NF-κB**
- **ZGA** was found to *down-regulate* transcriptional activity of **NF-κB**.
- Western blotting and immunohistochemical analysis indicated a reduction of **CXCR4**, **NF-κB**, and **Ki67** in tumor tissues.
- **ZGA** presented *good inhibition* of **tumor growth** and **liver/lung metastasis** in mice model.

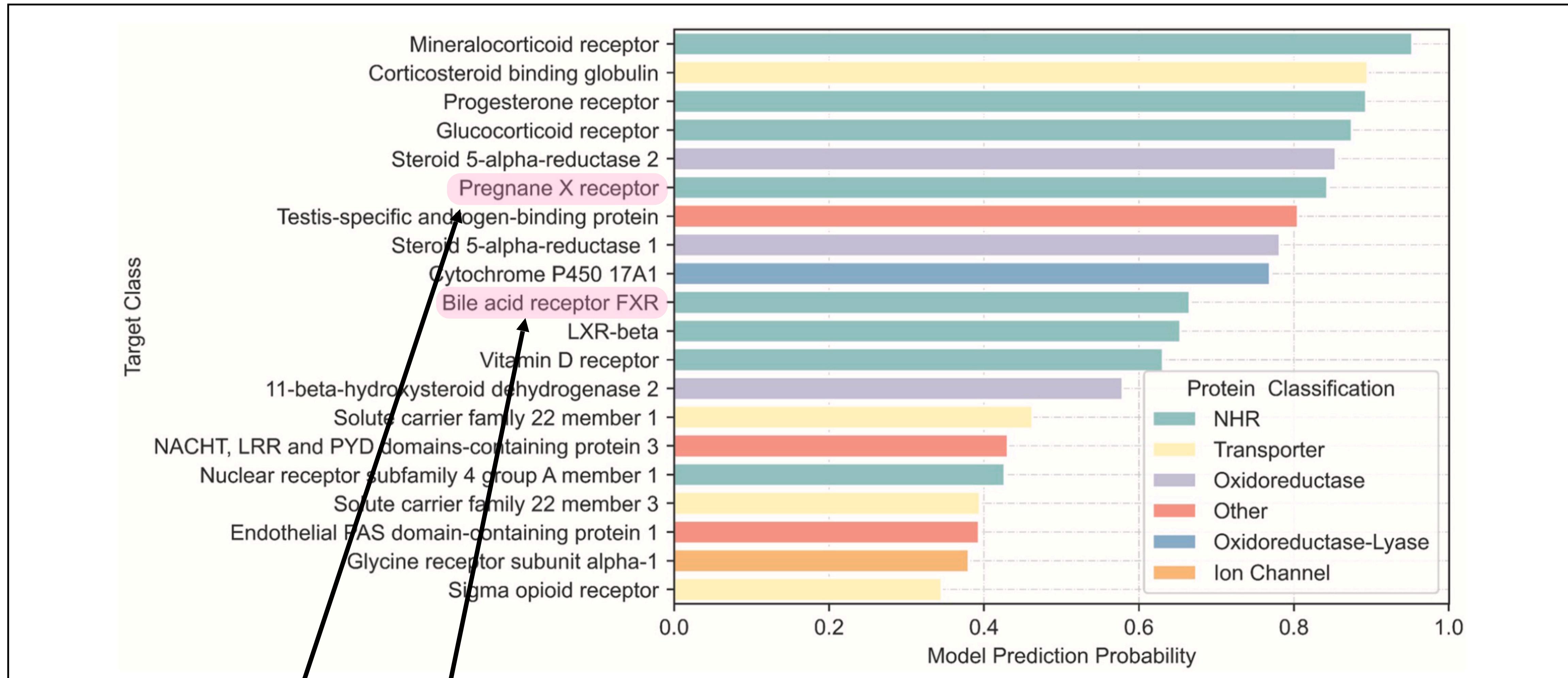
How ?

Mode-of-Action Analysis

Ligand-Target Prediction model activity probability predictions at a 10 µM threshold, sorted by decreasing probability. Values describe the confidence of the model of activity at this threshold, given the data used for training.

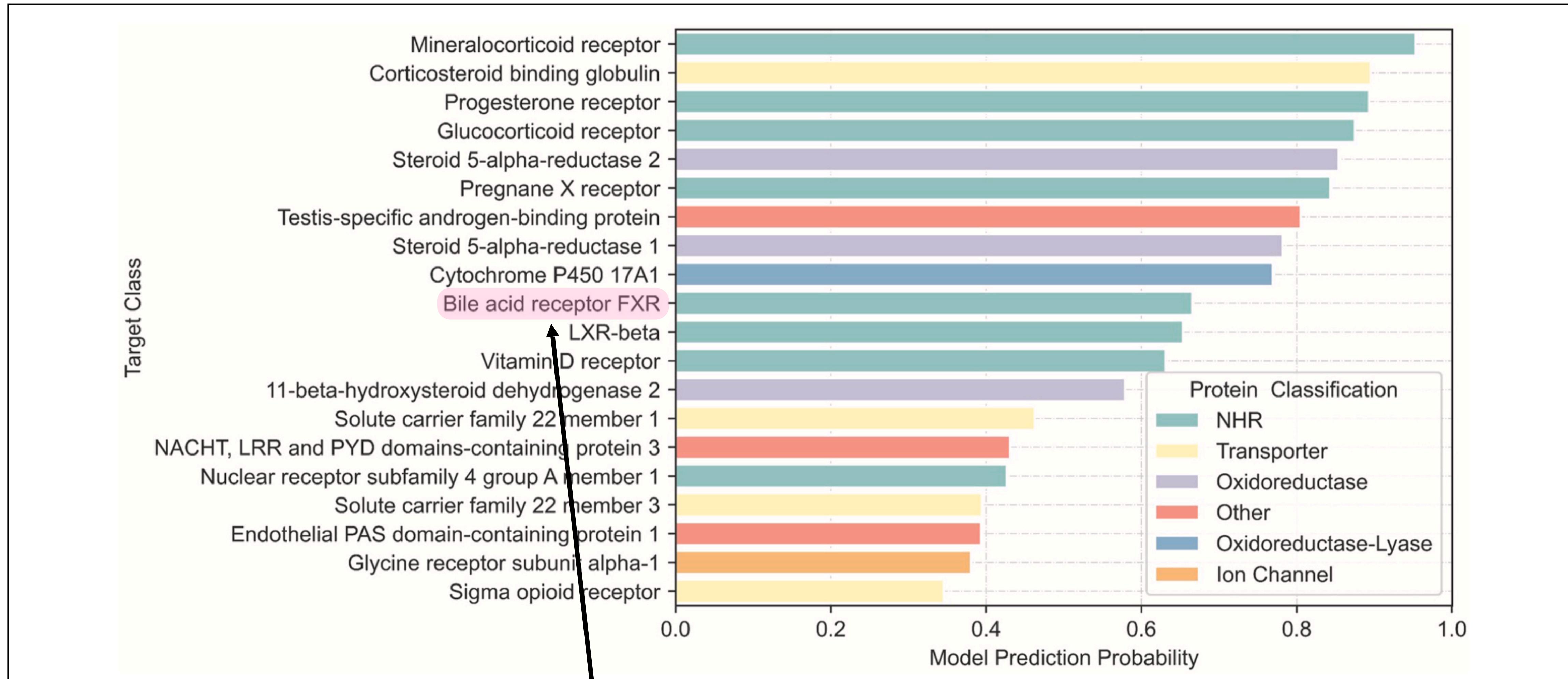


Mode-of-Action Analysis



PXR and FXR have been linked with functional impact on NF-κB.

Mode-of-Action Analysis



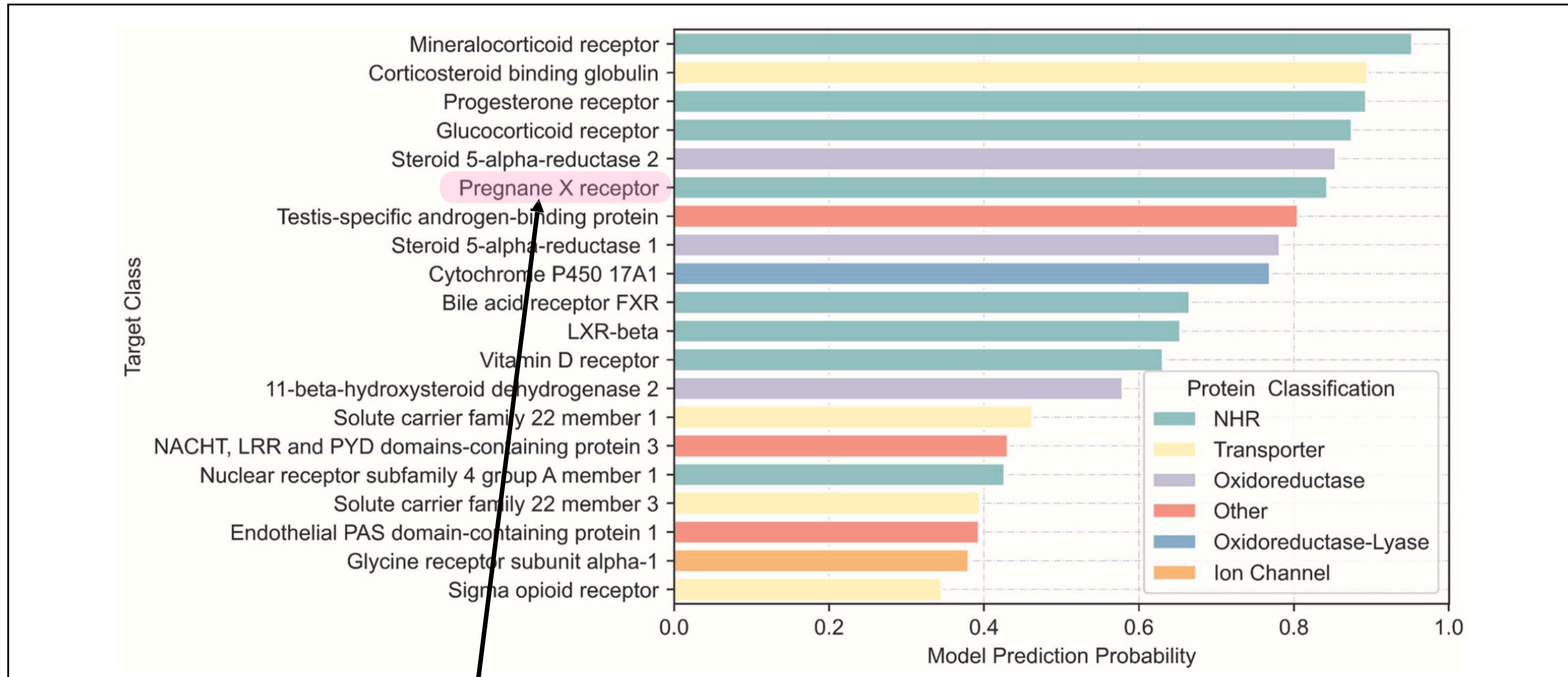
ZGA is an antagonist of FXR with an IC₅₀ value of 10 μM (Nam et al., 2006).

Mode-of-Action Analysis

Results

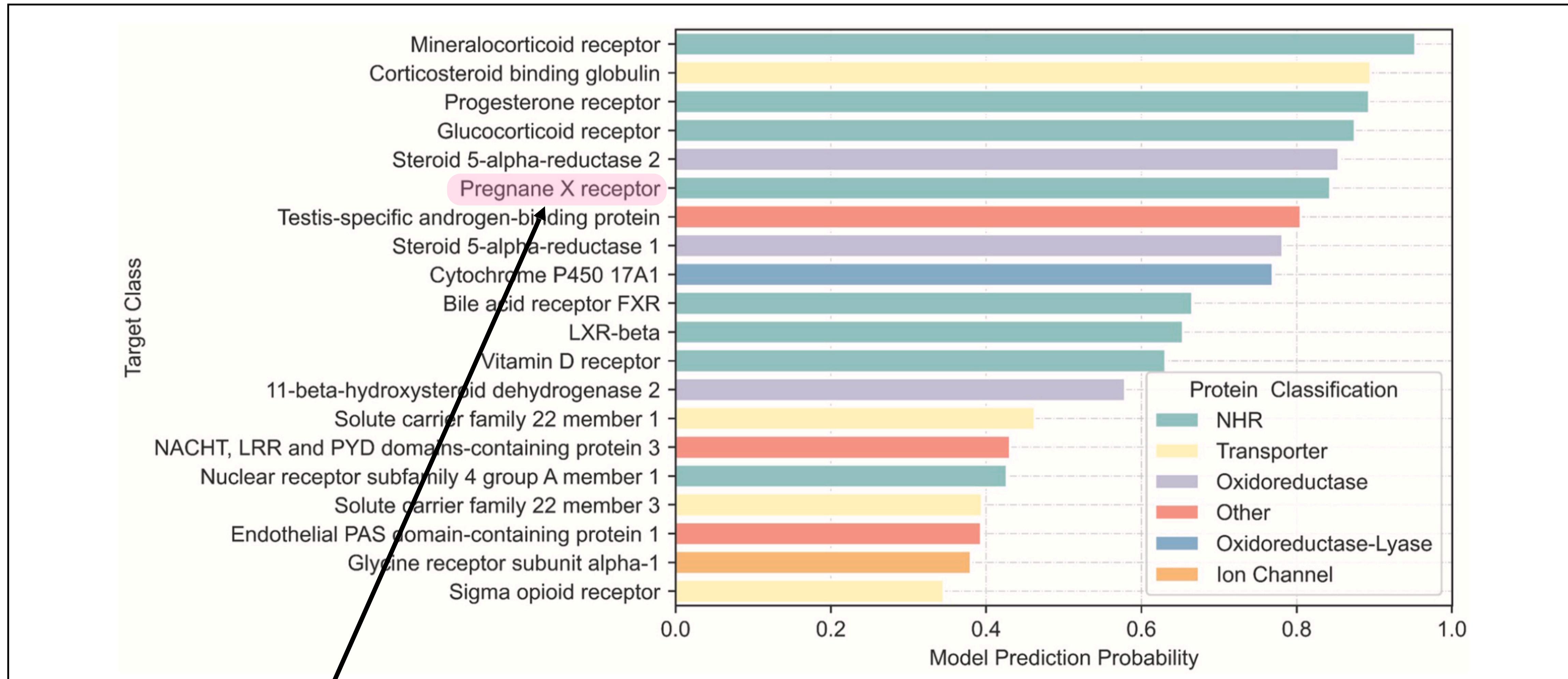
- In **FXR** over expressed cancers, *antagonist* treatment lowers proliferation, migration, and invasion whilst leading to apoptosis (Girisa et al., 2021) which is consistent with the effects and mode-of-action of ZGA in the current study.

Mode-of-Action Analysis



ZGA is also an agonist of PXR (IC₅₀ = 2.4 nM) (Meyer et al., 2005; Owsley and Chiang, 2003).

Mode-of-Action Analysis



PXR agonism has been related to the down regulation of **NF-κB**
(Schmuth et al., 2014; Zhou et al., 2006).

Mode-of-Action Analysis

Conclusion

- Computational analysis suggested **PXR agonism** and **FXR antagonism** as targets of ZGA.
- Computational target prediction suggested direct targets of **ZGA** related to **NF-κB** down regulation, which were also directly supported by experimental evidence for this compound.
- **CXCR4** was found to be over-expressed in majority of patient-derived TNBC tissues.
- **ZGA** abrogated the growth of TNBC tumors by partly targeting the **CXCL12/CXCR4** signaling axis.

Fin.

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