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## Fragment-based Discovery Aiming at a Novel Modulation of Malate Dehydrogenase and Beyond

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# Propositions

for the thesis

## Fragment-based Discovery Aiming at a Novel Modulation of Malate Dehydrogenase and Beyond

Atilio Reyes Romero

1. Malate dehydrogenases (MDH) is a hyper-expressed enzyme in pathological conditions like cancer. To date, all MDH antagonists belong to the class of competitive inhibitors, thus exposing the treatment to off-target effects.
2. Fragment-based high throughput screening is an efficient workflow to discover fragments binding at the oligomeric interfaces, thus offering an acceptable alternative to therapeutically relevant enzymes.
3. Macrocycles pushes beyond the limits of the “druggable” chemical space. Nevertheless, the major issue in predicting their bioactive conformation is represented by the constrained flexibility of the ring.
4. Covalent inhibition confers unlimited or very high affinity, even for a small compound, while leaving a main issue for selectivity/off-target labeling.
5. Protein-tyrosine phosphatase 1B (PTP1B) is a validated drug target for diabetes and obesity and plays a critical role in pancreatic cancer. However, due to the highly polar phosphatase active site and the shallow nature of the surrounding protein surface, inhibitor progression to clinical trials has proved very difficult, and so far, no drug is on the market.
6. The use of gliptins in patients with COVID-19 can offer a simple way to reduce the virus entry and replications.
7. A scientific project shares several features with a *mise-en-place*: not only it requires a meticulous preparation of the ingredients around a dish but also that the *chef de cuisine* has been prepared well in advance for any situation that may logically occur during the service.
8. “Success is all about going from failure to failure without losing enthusiasm.” [Winston Churchill]
9. “You cannot hope to build a better world without improving the individuals. To that end, each of us must work for our own improvement.” [Marie Skłodowska- Curie]
10. Always be curious.