# Nsp15 Target Meeting

February 13th, 2024

## Action Items

* Da to test some more plates and to do dose response on possible hits
* Xin to finish chemistry of compounds and send to Inna- also send compounds that are being shipped to UCL

## Meeting Notes

[Screening Efforts- Da](https://adminliveunc.sharepoint.com/:p:/r/sites/READDI-AC-Project1-CoronavirusProtease/Shared%20Documents/Project%201-Coronavirus%20Protease/Krieger%20MP/02_13_2024/Nsp15_update_feb2024.pptx?d=w85312cae5f3240b0aac16b96face03d5&csf=1&web=1&e=D4qlQu)

* Da screened 6,400 compounds in SAC2
  + Will retest some plates that have artifacts, but overall did not have any hits that inhibited
* Also screened ~10k compounds in Sac3
  + Most plates had no hits- plates with 1 or 2 hits will be tested in dose response and some will be retested to remove false positives
* Co-crystallization
  + Still working on SACC-0071929 and SACC-0333084 series
    - Out of this same series, tried co-crystallization and co-soak with a different molecule- this showed poor solubility
  + Two more compounds were crystallized (SACC-0116360 and SACC-0119065) in presence of compound and then soaked- these will be repeated, because there was a resolution issue
    - Could do diffraction to see if there are any extra densities in the active site
* Syncotron in US is still down for a few months in Chicago- will be back online this year, but causing a bit of a hold up

[TAMU Chemistry Update- Radha](https://adminliveunc.sharepoint.com/:p:/r/sites/READDI-AC-Project1-CoronavirusProtease/Shared%20Documents/Project%201-Coronavirus%20Protease/Krieger%20MP/02_13_2024/RB-NSP-15%20Updates.pptx?d=w077a7c32ff78431496586abd172f196f&csf=1&web=1&e=gdUscE)

* Synthesized 3 analogs- 2 analogs are not active
* Working on changing some functional groups of the starting compound to see how activity changes
* The starting compound has poor solubility

[Nsp15 protein production and assay development- Jelena](https://adminliveunc.sharepoint.com/:p:/r/sites/READDI-AC-Project1-CoronavirusProtease/Shared%20Documents/Project%201-Coronavirus%20Protease/Krieger%20MP/02_13_2024/JT_20240213_nsp15_project%20meeting.pptx?d=wced437d572724164b078619f6d5a893f&csf=1&web=1&e=e78BVQ)

* Added additional amino acids and went through first round of purification; waiting on final MS data to confirm
* By end of this month, will be ready to screen
* Can do binding testing with NMR- could be interesting

[UCL Chemistry Update-Xin](https://adminliveunc.sharepoint.com/:p:/r/sites/READDI-AC-Project1-CoronavirusProtease/Shared%20Documents/Project%201-Coronavirus%20Protease/Krieger%20MP/02_13_2024/Xin_13022024.pptx?d=w7f71a80713cb4d90a17ecf740551eedb&csf=1&web=1&e=msYDcD)

* Initial two hits had low solubility, so Xin tried to expand
  + Did modification on triazole part and linkers
  + Nick Heaton’s lab tested these two compounds as well and had decent inhibition of nsp15 at 25uM
* Molecules are coming to UCL and then will be sent to Inna for testing; other compounds are being purified by Xin and will also be sent
* Also working on in house synthesis that will also be sent to Inna

Strategy Discussion

* Screening vs. Chemistry on hits in original assay
  + More data hits have been generated by Da- there will be some retesting and some dose response before we can make a decision
* If we can keep screening at a decent rate while also doing chemistry in parallel, that would be an ideal path forward
  + First priority is to finish the screen, and if we can get some decent compounds along the way for chemistry, that would be ideal
* There are 130k compounds to screen and we have screened ~1/5 of the library so far; can do ~10k a week
* 7 compounds were sent to Sara Cherry from Core D for antiviral testing and non were active at 20uM screened against SARS-CoV-2 in A549 cells; no toxicity either