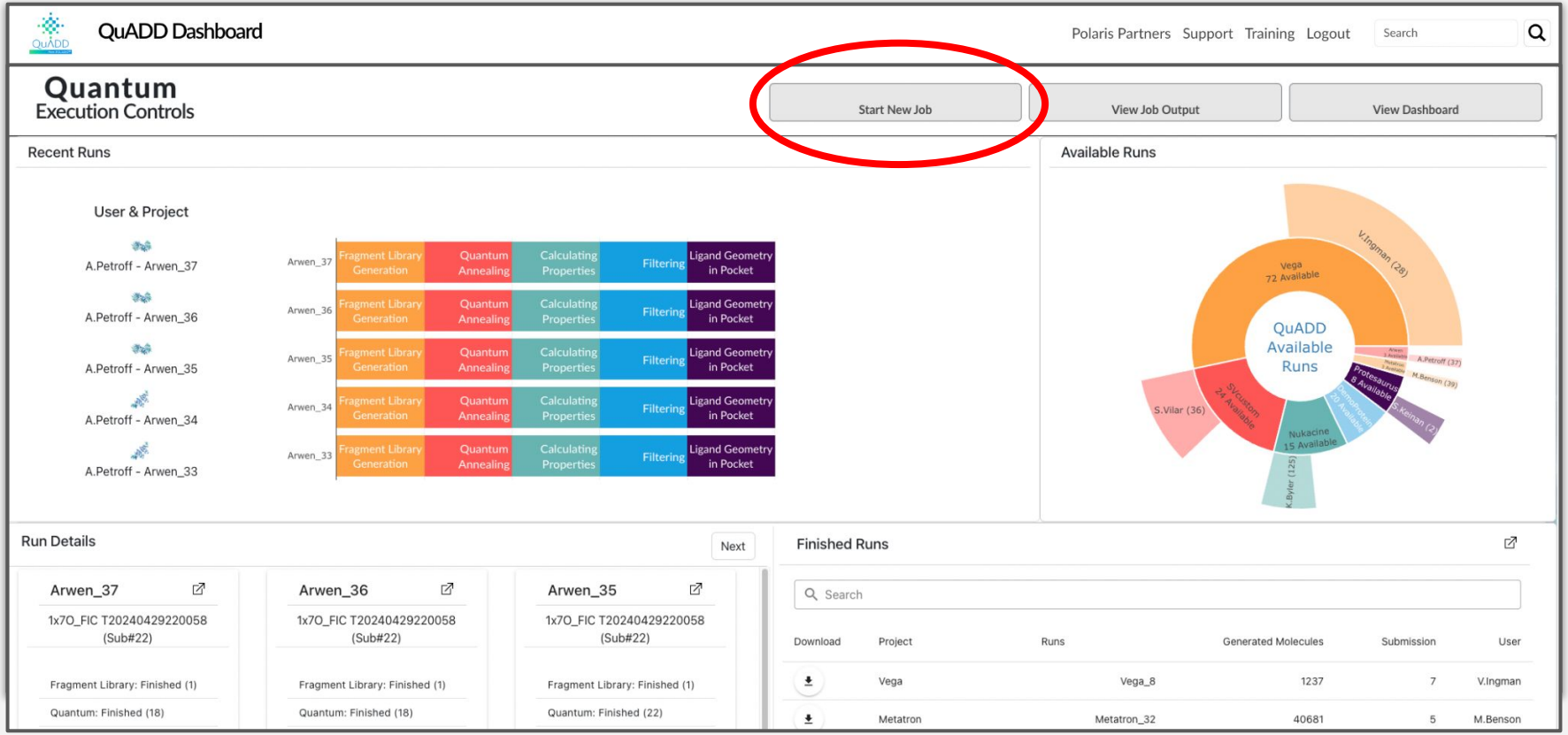
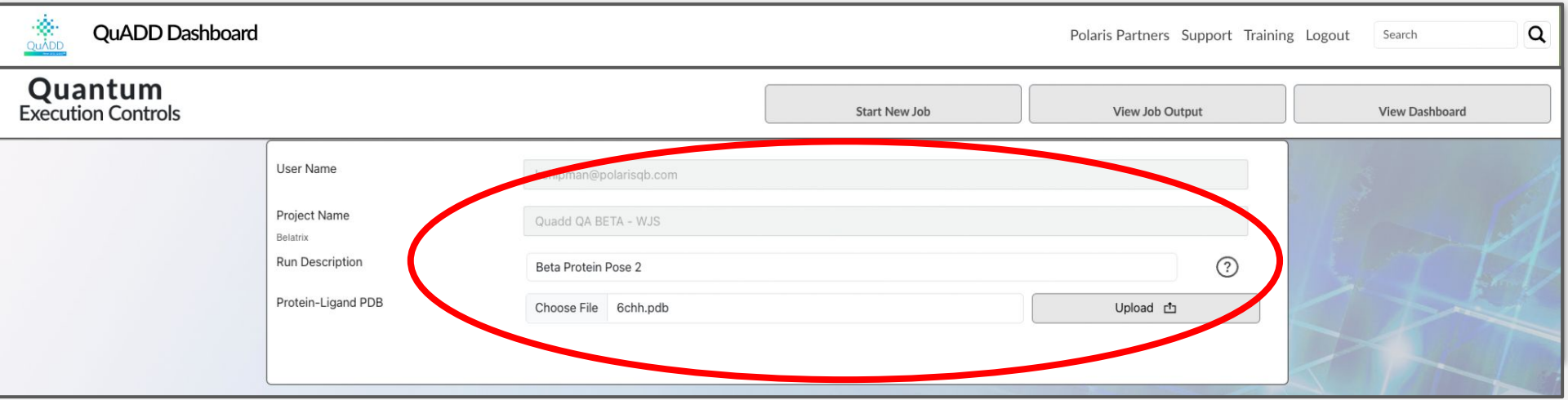
Launching a new job on QuADD
07/08/2025

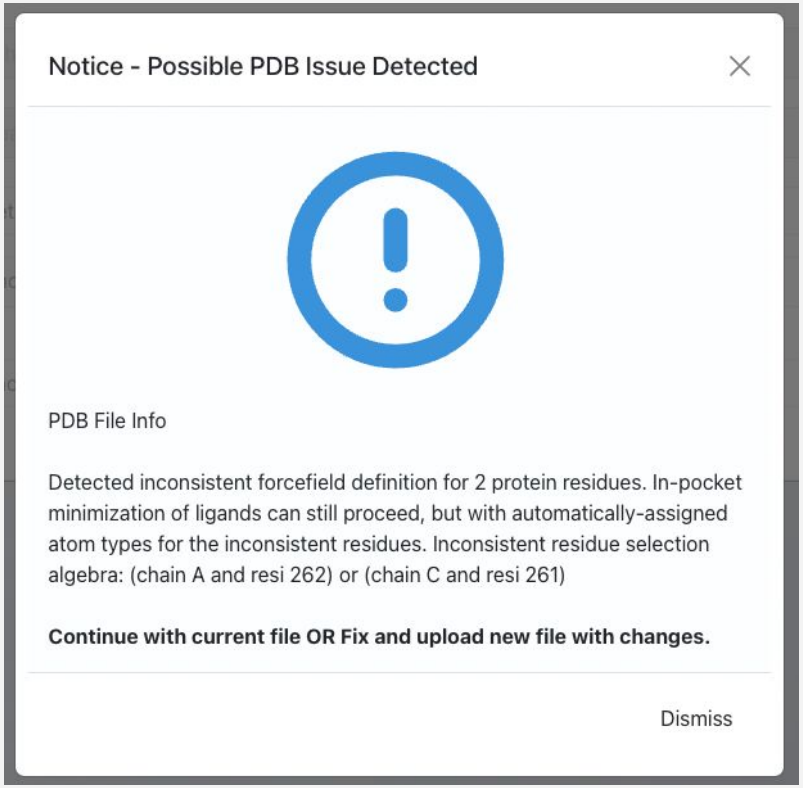


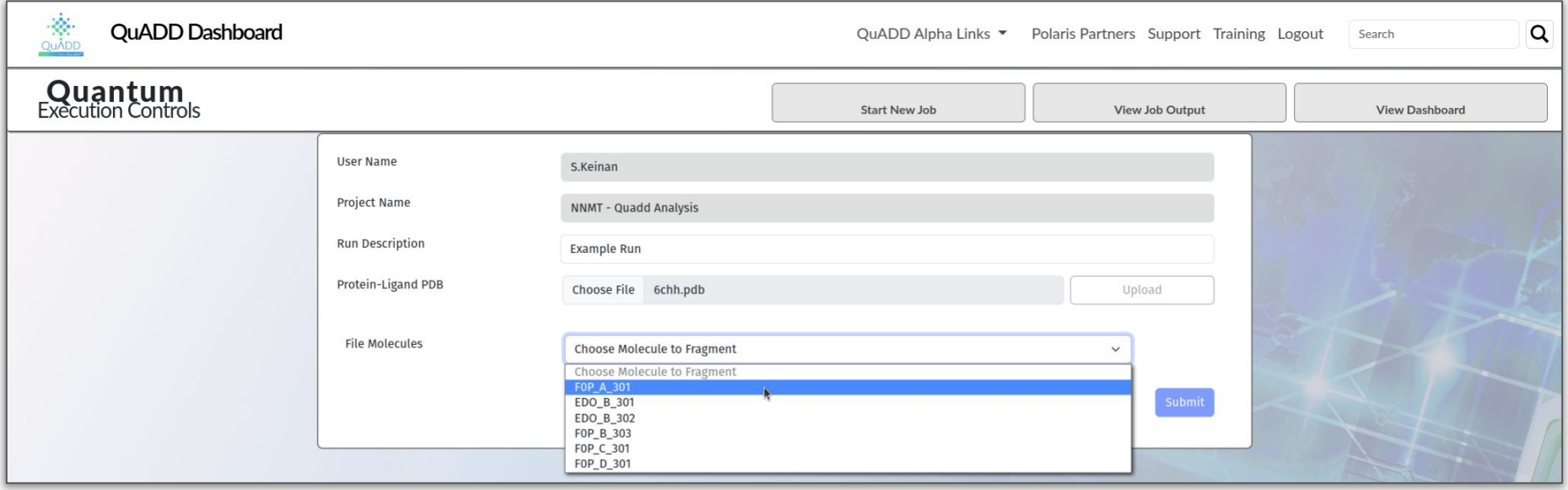
- Click the "Start New Job" button to begin your submission



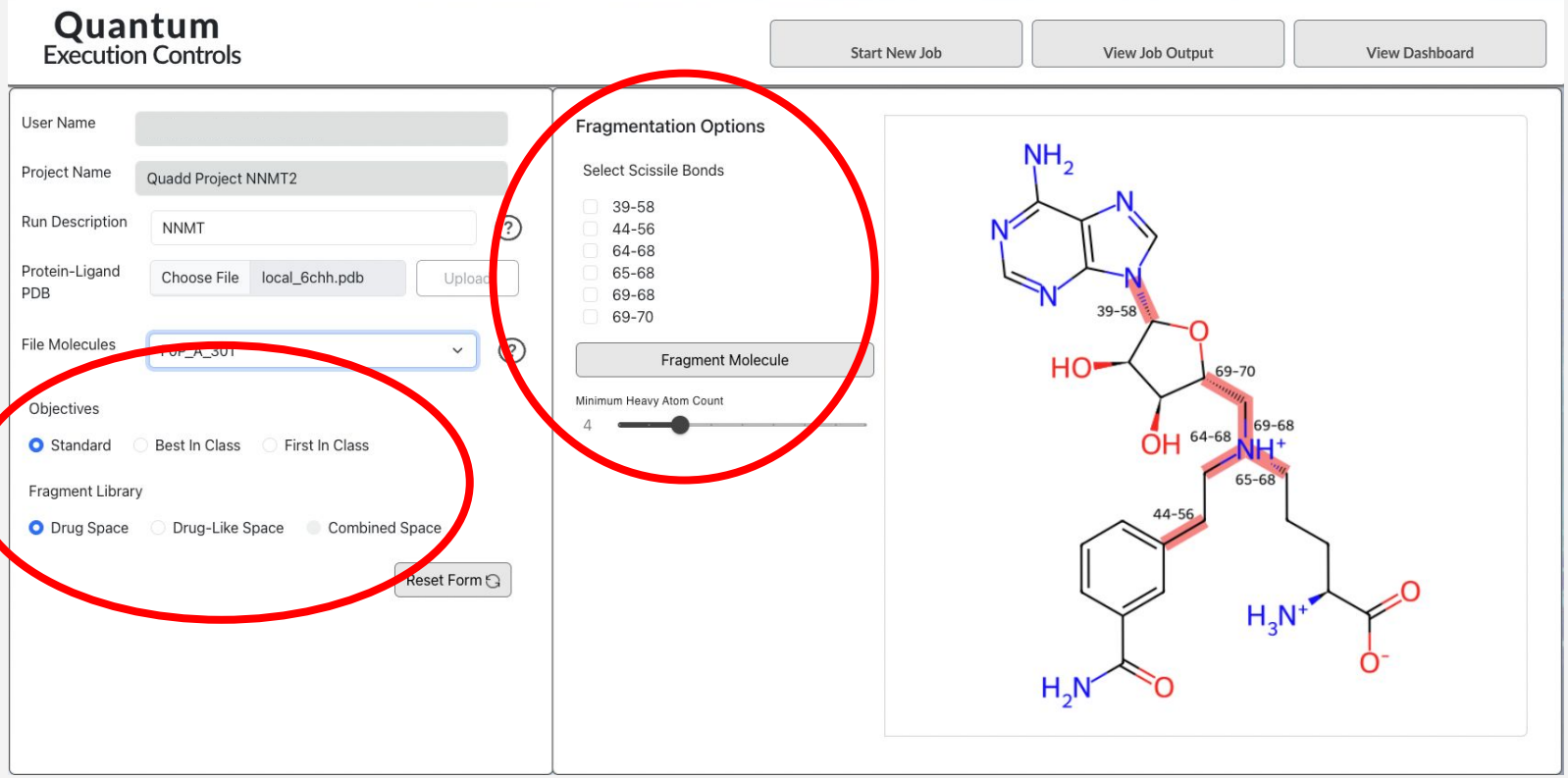
- Select your account under “Project Name”
- Enter a description for the run
- Use the "Choose File" dialog to select a Protein-Ligand complex PDB from your computer
- Click the "Upload" button
- QuADD will attempt to fix any detected issues with your input PDB, but using a PDB that has already been cleaned and protonated is preferred. It is also suggested to trim any unneeded chains prior to upload.

- In the input uploading process QuADD checks the input in a variety of ways
- One common occurrence is shown in this **Alert Box**
- This alert describes what was detected and provides references to the residues in PyMOL selection syntax
- Alternative you may see a message indicating the input was not able to be processed (**PDB Cleaning Failed**), please contact help@quadd.bio for more assistance



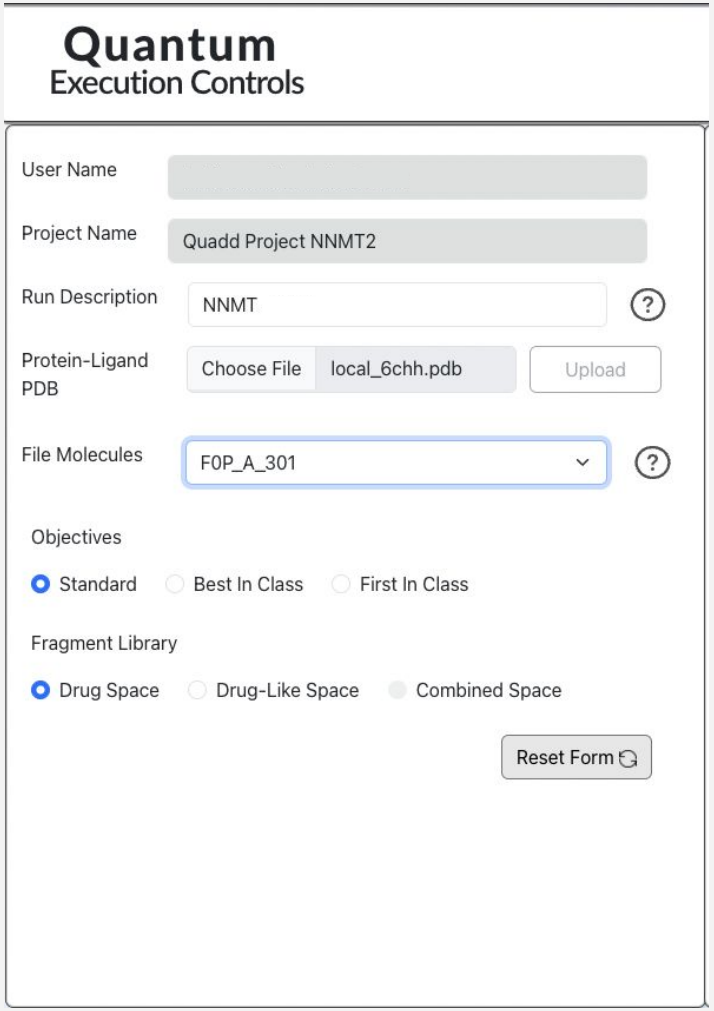


- Your PDB will be searched for small molecules
- Choose the ligand of interest from the dropdown menu
- The ligand names are built from the residue name, chain ID, and residue ID, as found in the PDB
- You will have the option to select another ligand on the next page

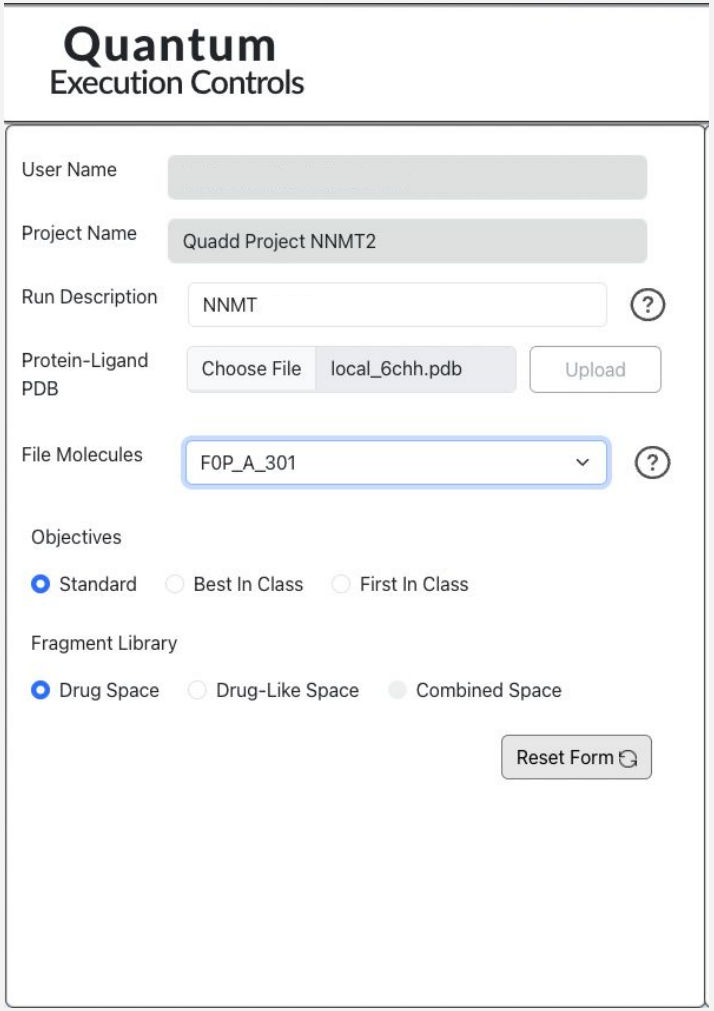


- Here you may choose your objectives, which fragment library to use, and various parameters for the fragmentation
- The highlighted bonds illustrate where the molecule may be split
- Some bonds may go unused depending on your fragmentation parameter selections (eg: the minimum heavy atom count can only be satisfied by excluding certain bonds)

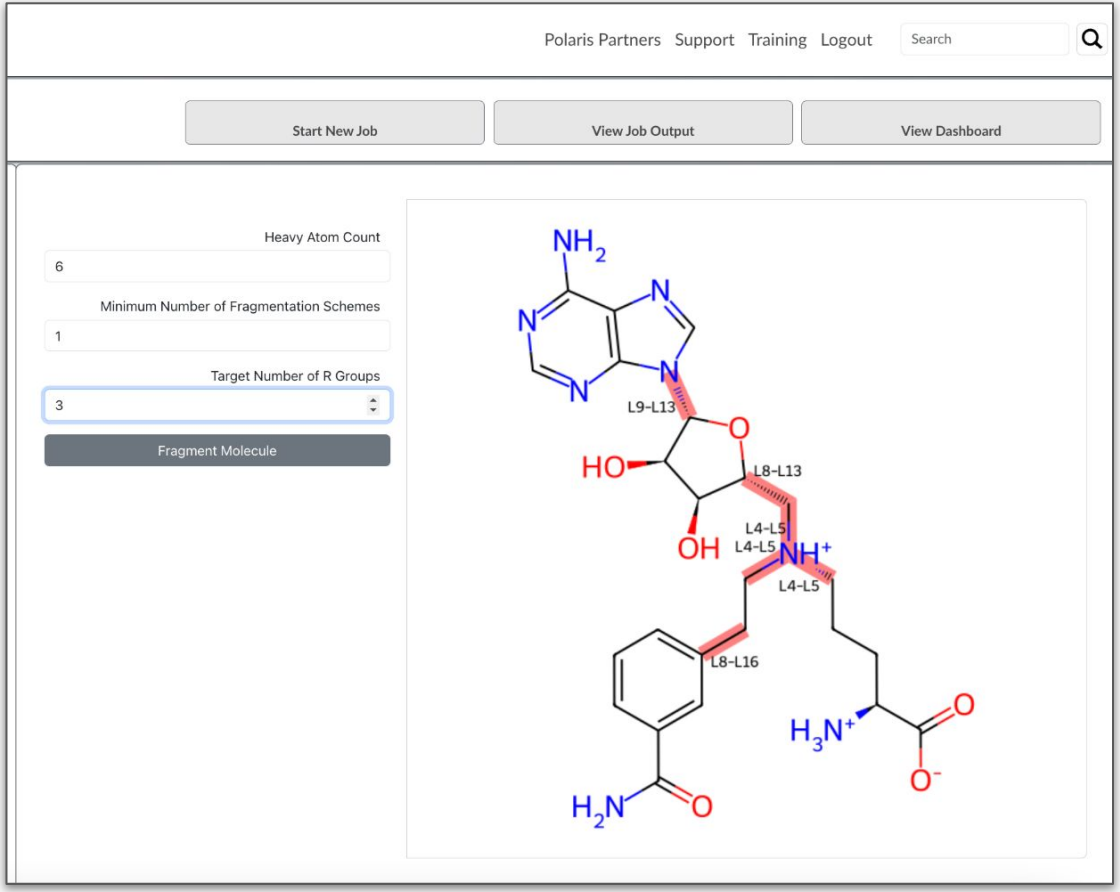
- Standard: Balance between diversity and similarity
- Best In Class:
  - Fragments will be chosen based on the starting ligand
  - Great for exploring similar binding modes, while still having good diversity
- First In Class:
  - Fragments will be chosen based on the starting ligand and the protein pocket
  - Good for exploring new binding modes
- Scaffold Hopping: Option to hold certain template fragments constant



- Standard: Balance between diversity and similarity
- Best In Class:
  - Fragments will be chosen based on the starting ligand
  - Great for exploring similar binding modes, while still having good diversity
- First In Class:
  - Fragments will be chosen based on the starting ligand and the protein pocket
  - Good for exploring new binding modes
- ~~Scaffold Hopping: Option to hold certain template fragments constant~~

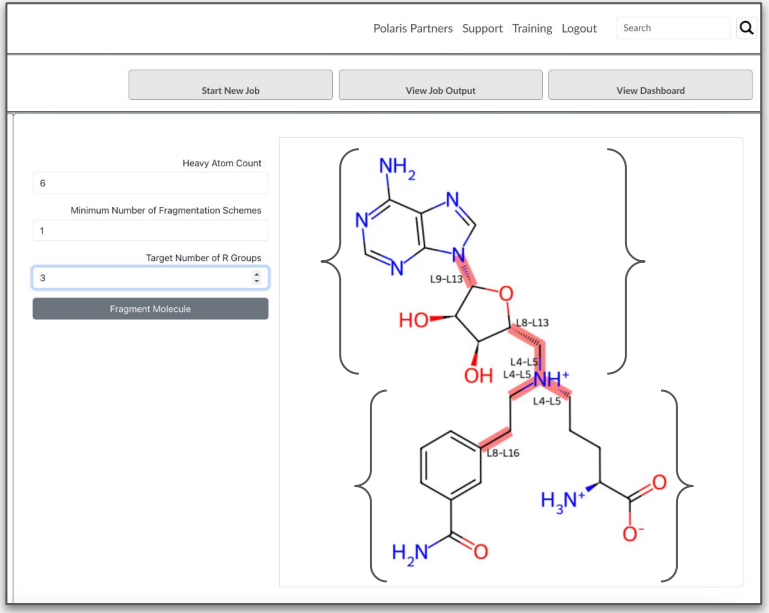


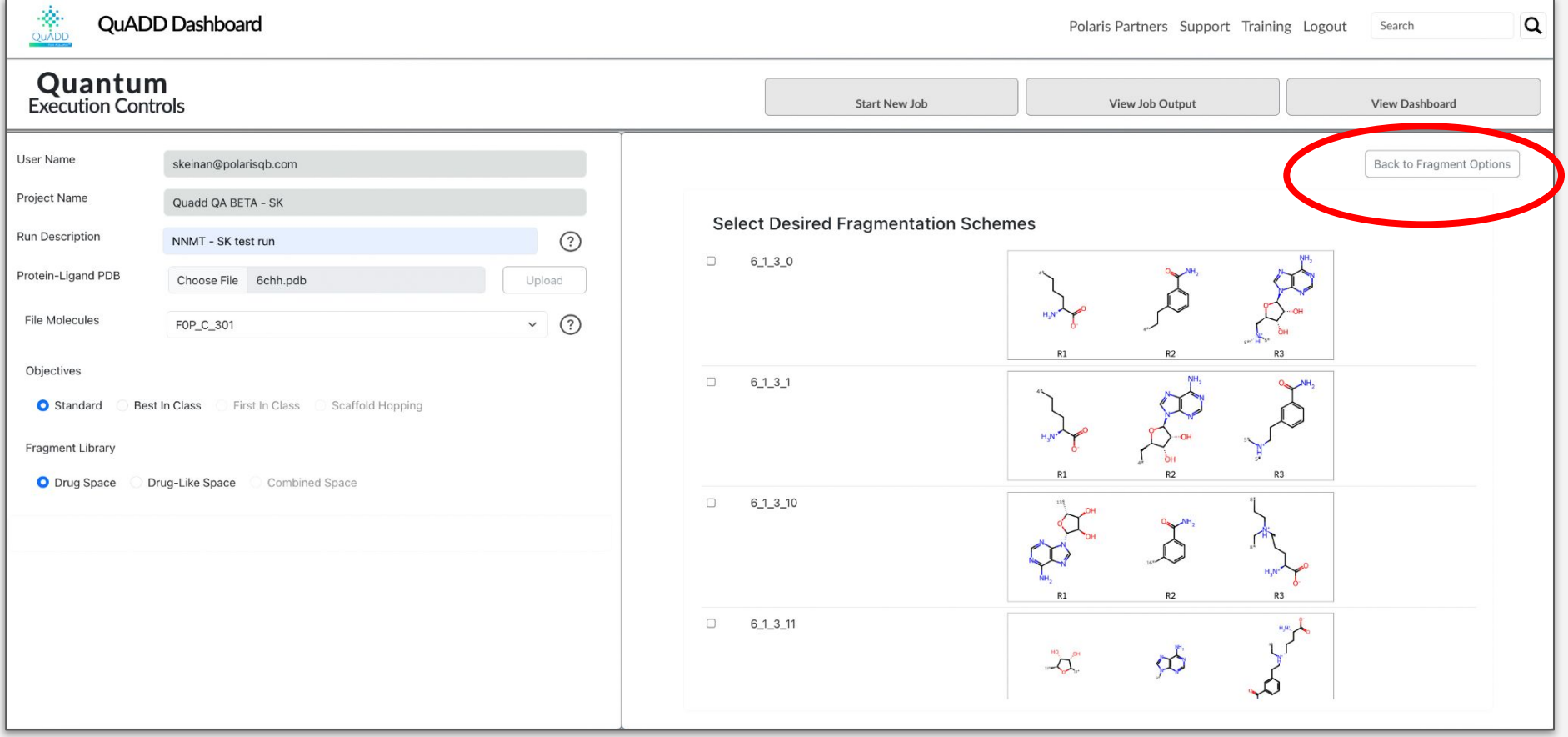
- Minimum Heavy Atom Count
  - Controls the size of fragments in accepted schemes
  - No smaller than 2 is advised
  - Between 2 and 4 is a good starting point
- Minimum Number of Schemes
  - If the number of schemes generated is less than this value, the Target Number of R Groups will be altered until enough schemes are produced
- Target Number of R Groups
  - The number of binding pocket sub-regions to consider in each scheme
  - Between 3 and 6 is a good starting point
  - It may be impossible to hit this number depending on the Minimum Heavy Atom Count chosen



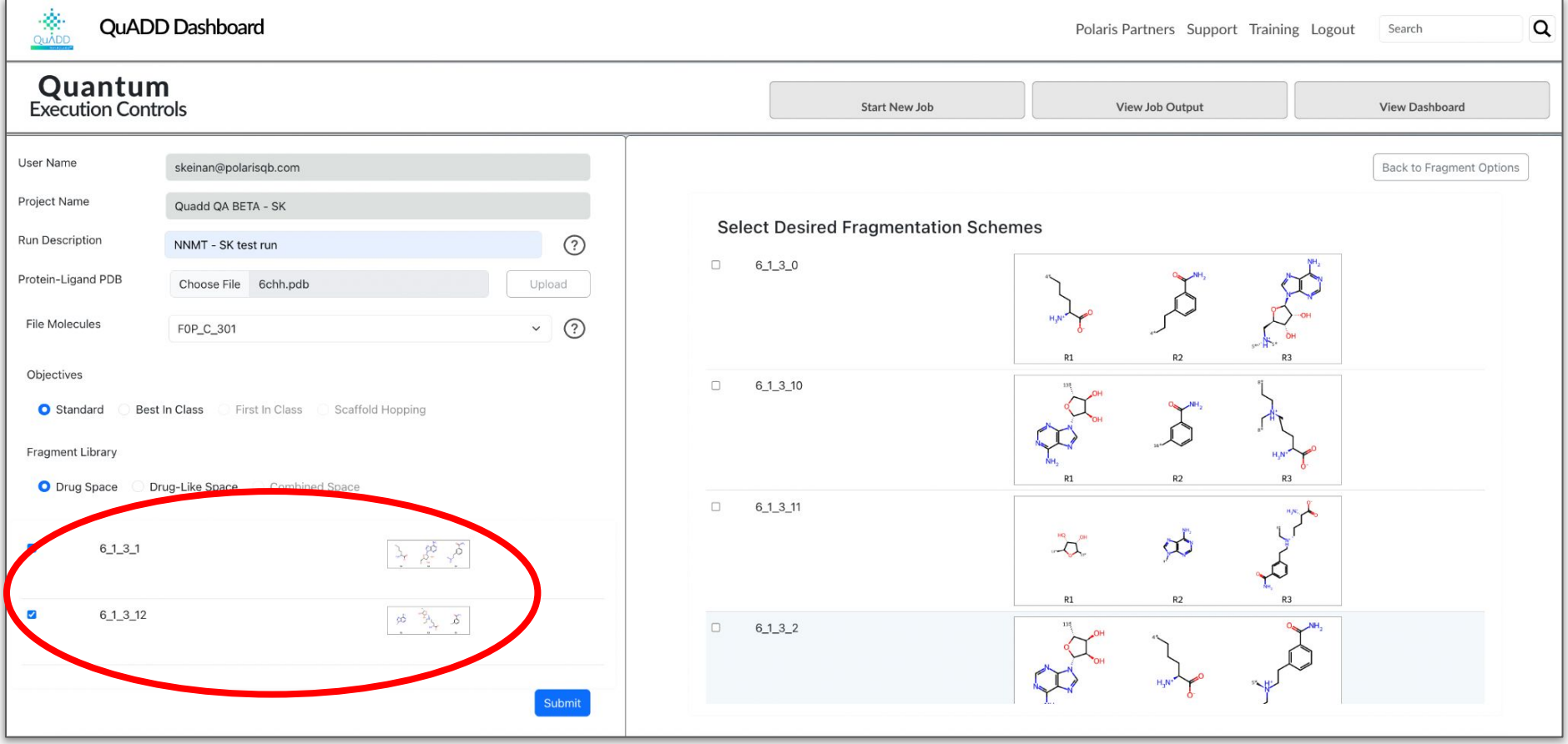
Choosing Fragmentation Schemes

Using a variety of fragmentation schemes for a given template molecule gives QuADD the best opportunity to return novel chemistry. Where the template structure follows a simple A+B+C construction of fragments, QuADD will return structures according to this paradigm. Where combinations of fragments are sought, *e.g.* (A+B)+C or A+(B+C), the fragmentation scheme manager allows for this level of detail in constructing QuADD molecules. And where a more complete scan of chemical space is desired, using several combinations of fragment schemes is suggested (<=10).



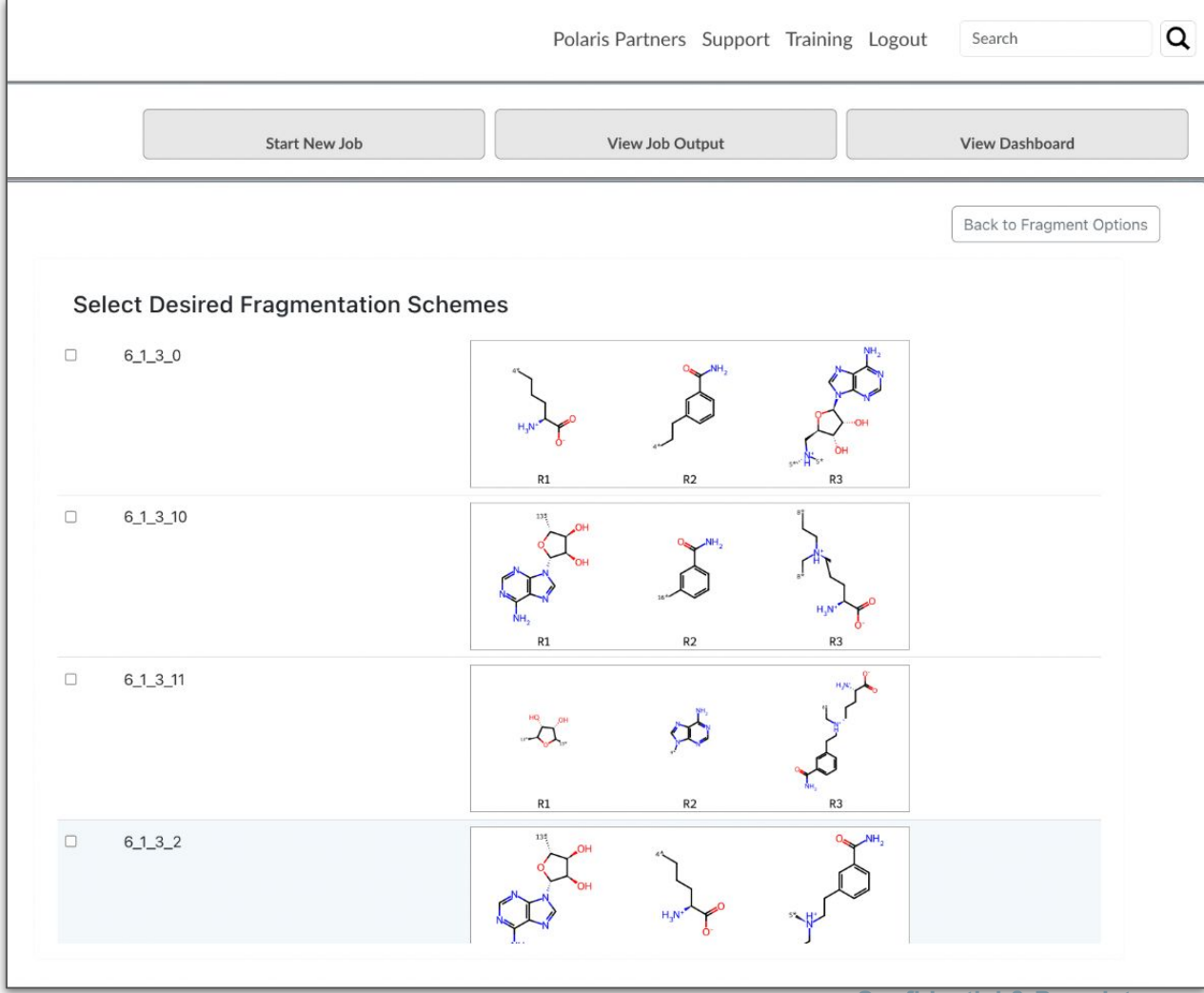


- If you need to change your fragmentation parameters, click Back to Fragment Options in the top right corner
- Fragmentation schemes are presented in QuADD's estimated best priority order

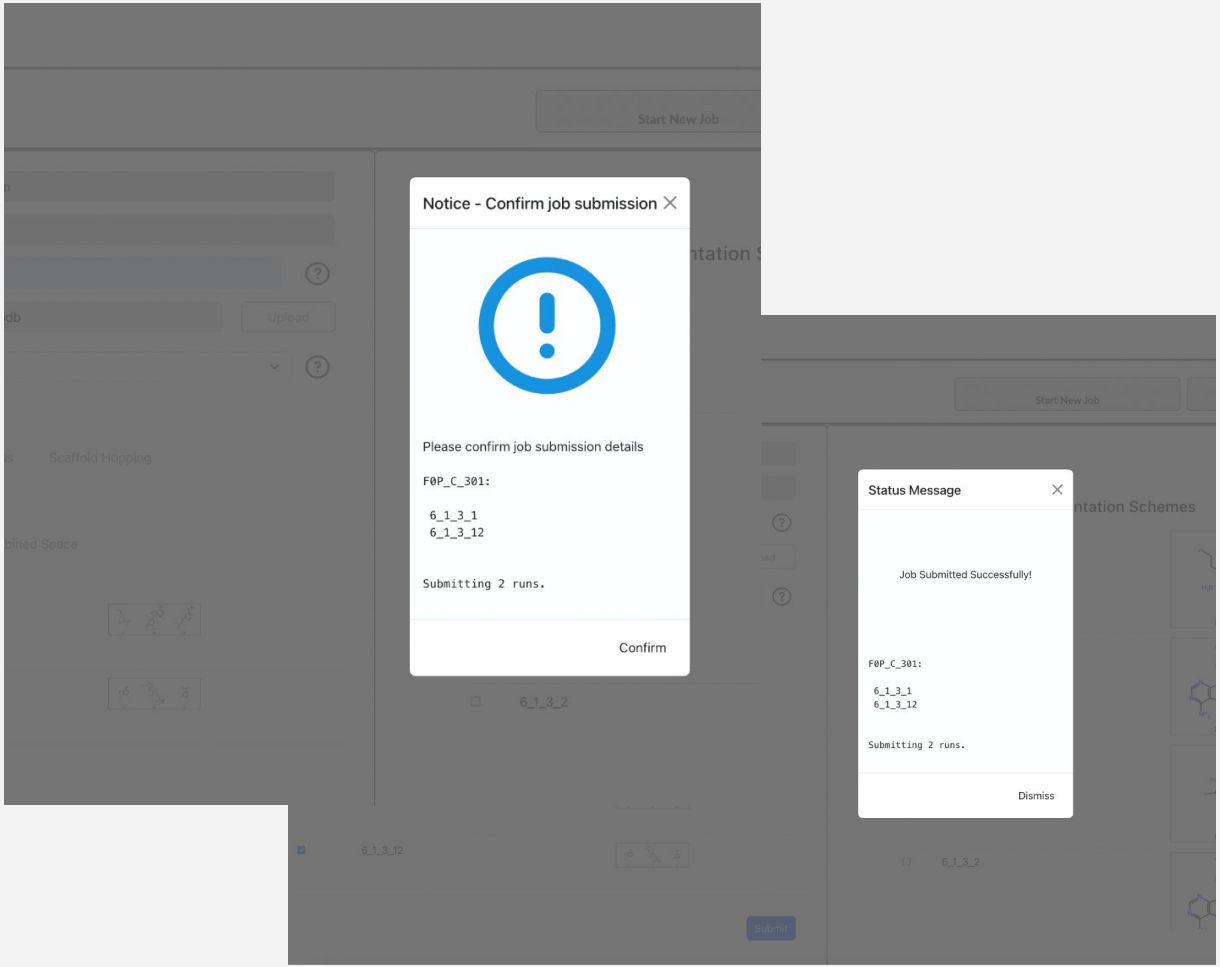


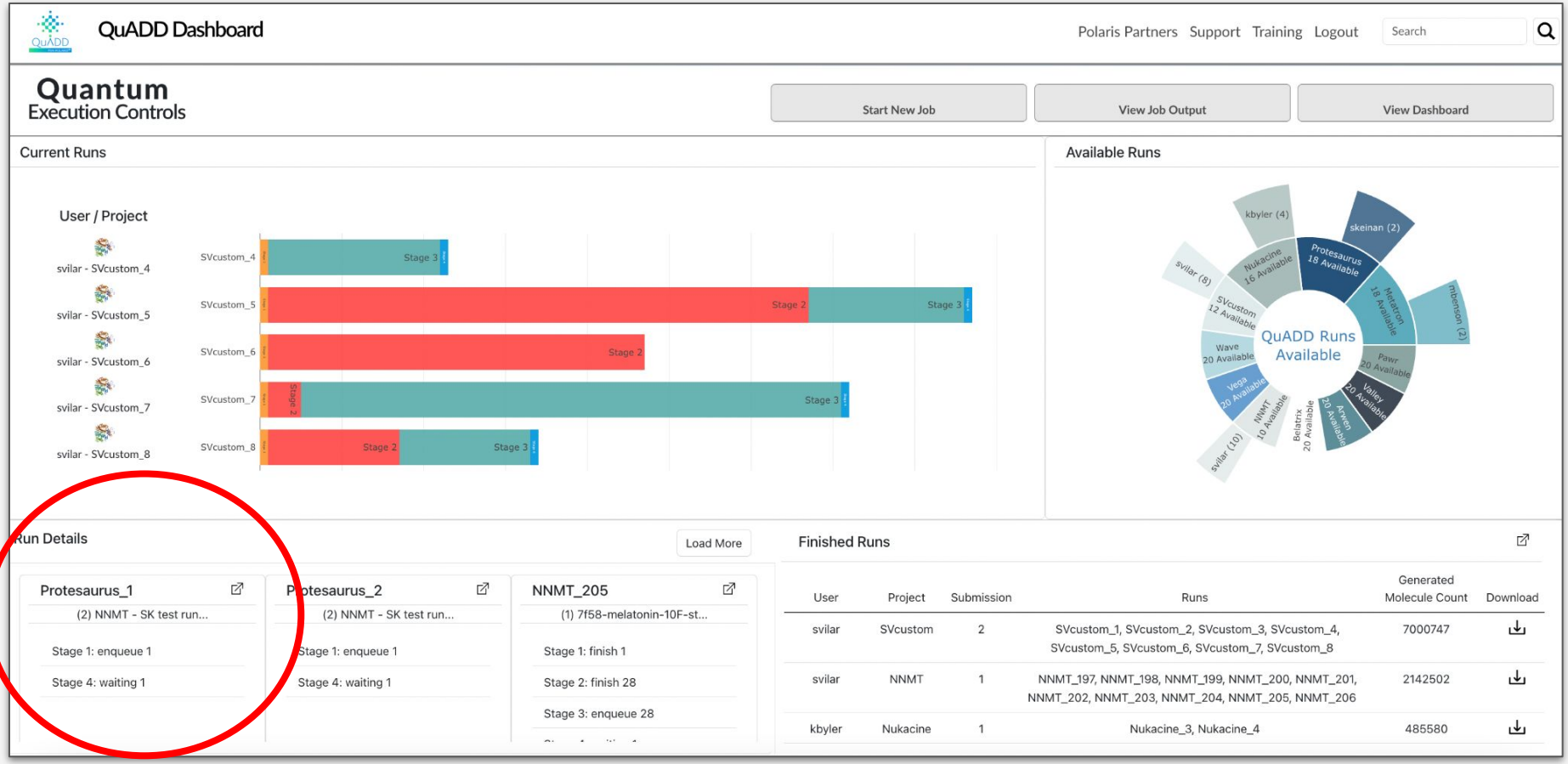
- Review and select from the generated fragmentation schemes
- Your schemes chosen for submission will be visible on the left

- You will be able to explore more chemical space by selecting different fragmentation schemes
- Tips for good scheme selection:
  - Varying the number of R Groups
  - Varying the number of connection points (noted with a "*") on analogous fragments
  - Functional moieties "moving" from one fragment to another or splitting alkyl chains at a different positions

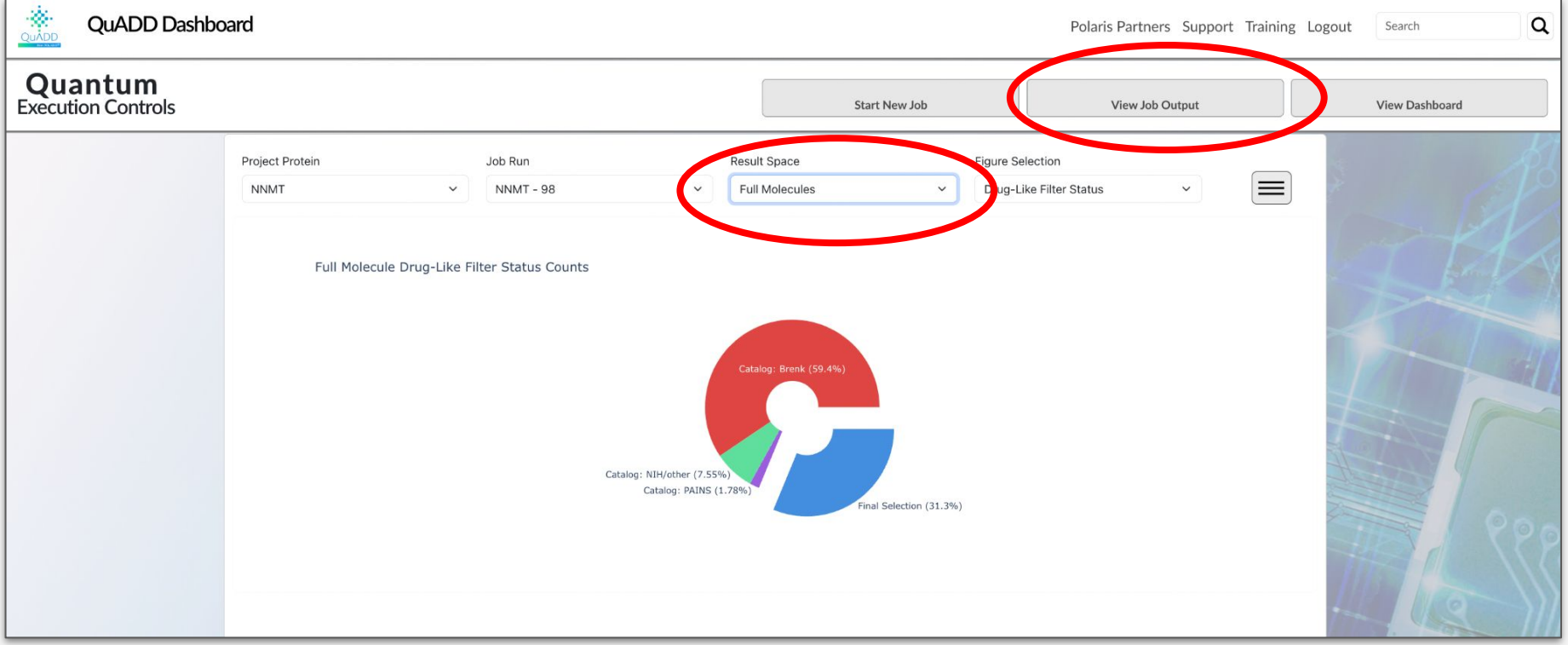


- Clicking the "Submit" button
- Confirm your selection
- You will be notified on successful submission
- Each fragmentation scheme is a separate run



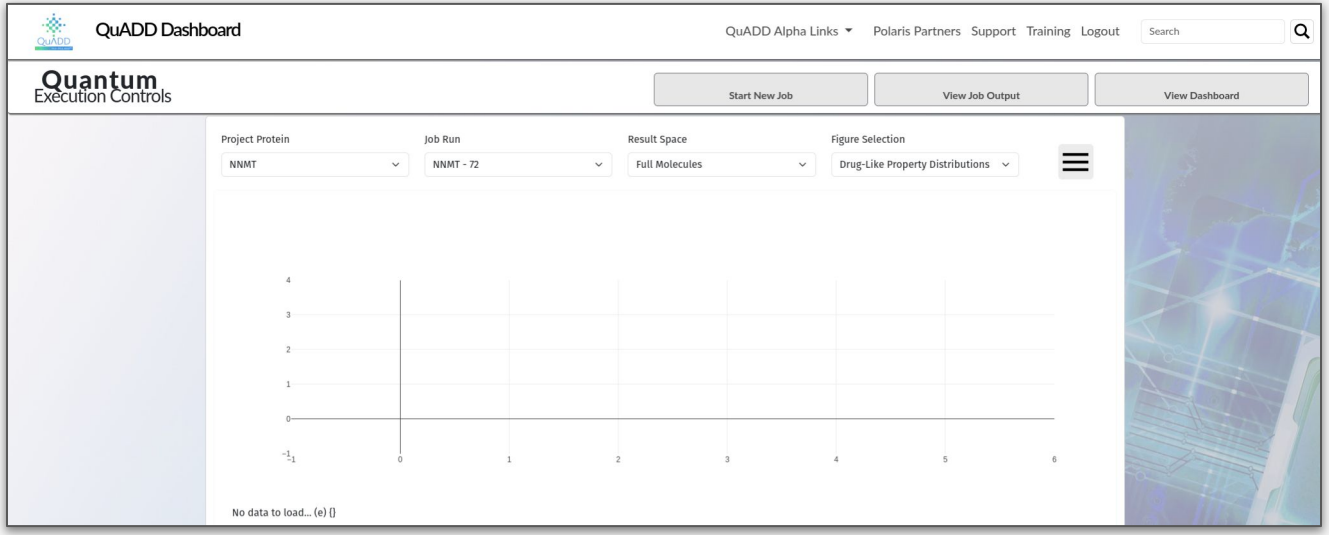


- You can see the submitted runs and follow the runs progress on the Dashboard



- Use the "View Job Output" button to explore various visualizations for the results of a single fragmentation scheme
- "Full Molecules" Result Space will give you plots relevant to the fully built molecules
- "Fragments" Result Space will provide plots where you can compare the performance of various R-Groups

- Some plots may not be available until the run has progressed further
- If you see a blank plot, check back later



- You can download results for individual runs here too

- Downloaded results are in a zip file
- Results contents:
  - SDF with 3D structures of your passing molecules
  - CSVs with molecule smiles and properties, one with all fully-built molecules and one with just the passing molecules
- "Passing" molecules are those within the bounds of the drug-like filters (Rule of 5 properties, unwanted substructures, PAINS, etc.)

Thank You for using QuADD

Please don’t hesitate to contact us if you have any questions

help@quadd.bio