Investigation of Inherited Cancer Associated PALB2 Variants

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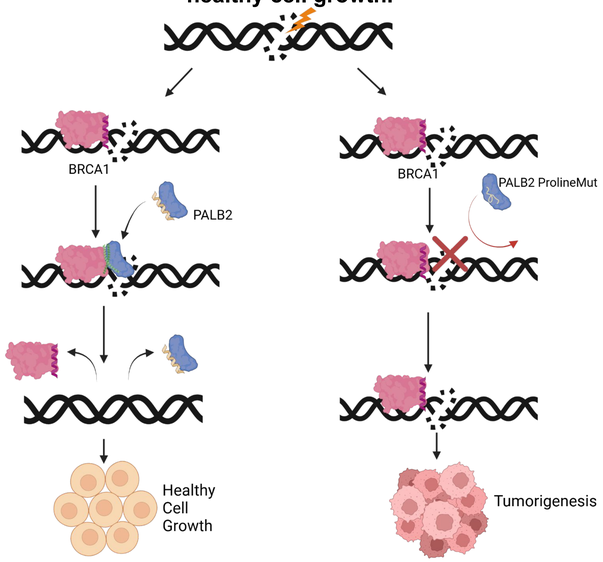
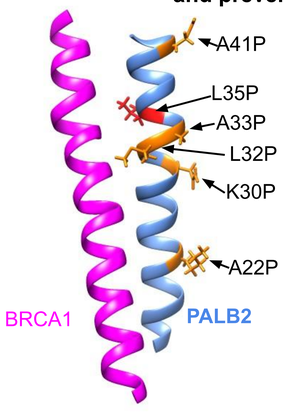
Introduction

PALB2 and BRCA1 interaction is vital for DNA damage repair and healthy cell growth.



Above left: Interactions between WT PALB2 and BRCA1 leads to the appropriate DNA repair response and health cell growth. **Above right:** Impaired interaction between PALB2 and BRCA1 due to mutated PALB2 structure leads to inappropriate DNA repair response and the development of cancer

Proline variants in PALB2 may destroy secondary structure and prevent binding with BRCA1



Left: Structure of the coiled coil regions of both PALB2 and BRCA1 with positions of PALB2 VUS labeled. L35P has been linked in multiple studies to the development of breast and ovarian cancer. However, it is unknown if it is due to a loss of critical binding residue or destruction of secondary structure due to the introduction of a proline. The other five VUS are also proline variants; it is unknown if they decrease binding and if they do if it is a result of the destruction of secondary structure.

Objectives

- Determine if the secondary structure is altered by proline mutations.
- Determine if secondary structure is vital to the coiled coils function.
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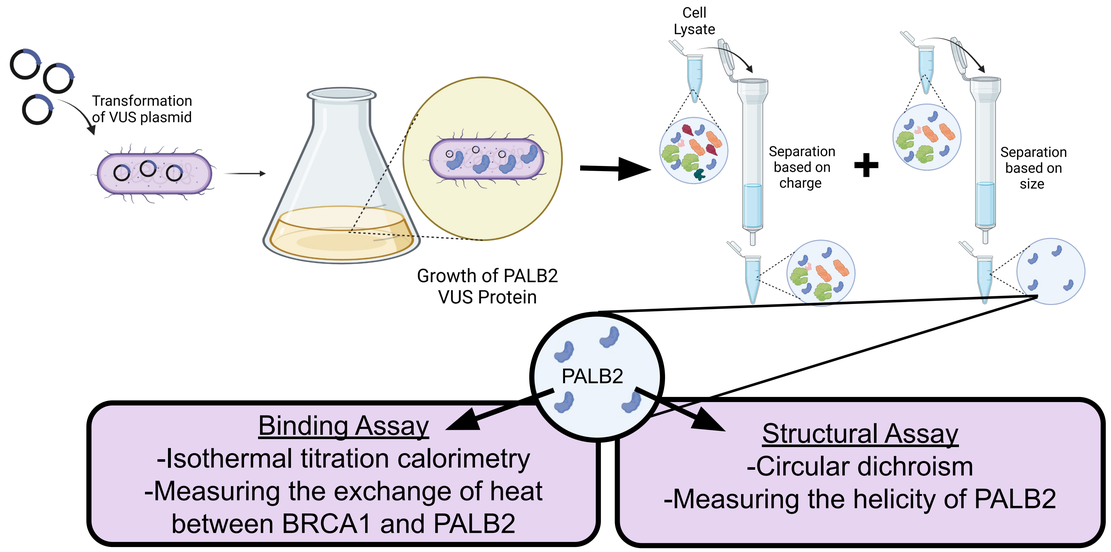
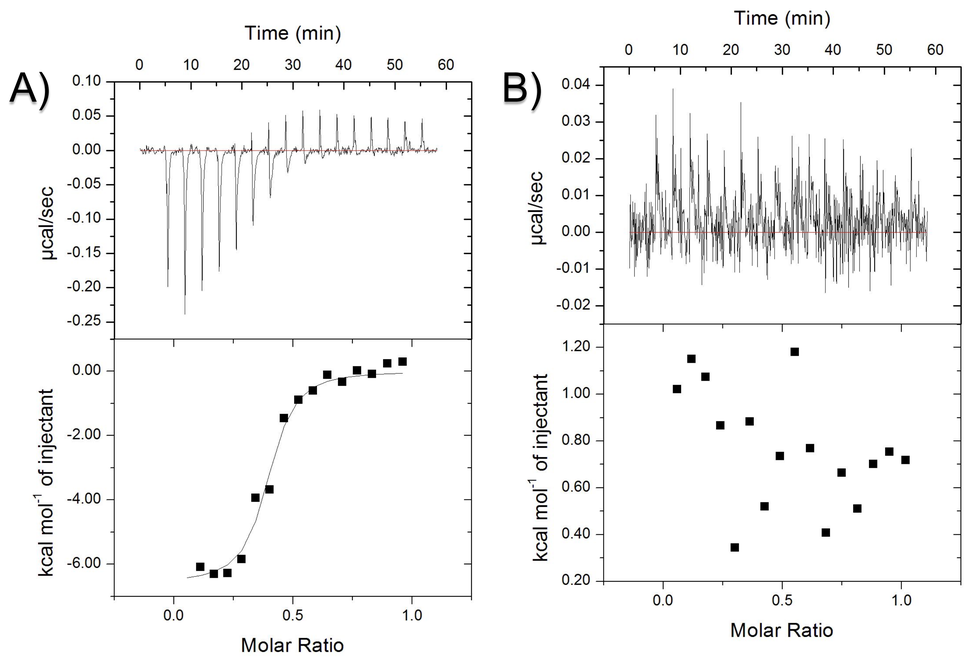
Purification and Structural/Binding Assays



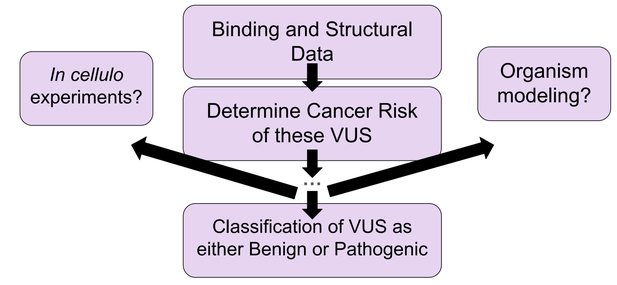
Patient Proline VUS Disrupt Heterodimerization



A) Isothermal titration calorimetry (ITC) profile of WT PALB2 titrated with BRCA1. The signature "S" curve displays that there is binding occurring between the coiled coil regions of PALB2 and BRCA1. **B)** ITC profile of K30P PALB2 titrated with BRCA1. The random heat signatures displays that there is no binding occurring between the two coiled-coil domains of the proteins, supporting our current hypothesis that these proline variants will disrupt binding with BRCA1.

Conclusions and Future Directions

Protein	Variant	Appropriate Binding to BRCA1	Coiled-Coil Disruption
PALB2	WT	✓	✓
PALB2	A22P	?	?
PALB2	K30P	✗	?
PALB2	L32P	?	?
PALB2	A33P	?	?
PALB2	A41P	?	?



- Currently we see that proline PALB2 VUS do lead to decreased binding; Will continue to proceed with ITC and CD experiments to categorize the rest of the variants in the above table
- Next Steps
  - Stability Assays to assess if stability is decreased by these variants

References and Funding

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