When Cancer Hides:
How CLL Cells Outsmart Treatment to Return and How to fight back with Smarter, Targeted Treatments

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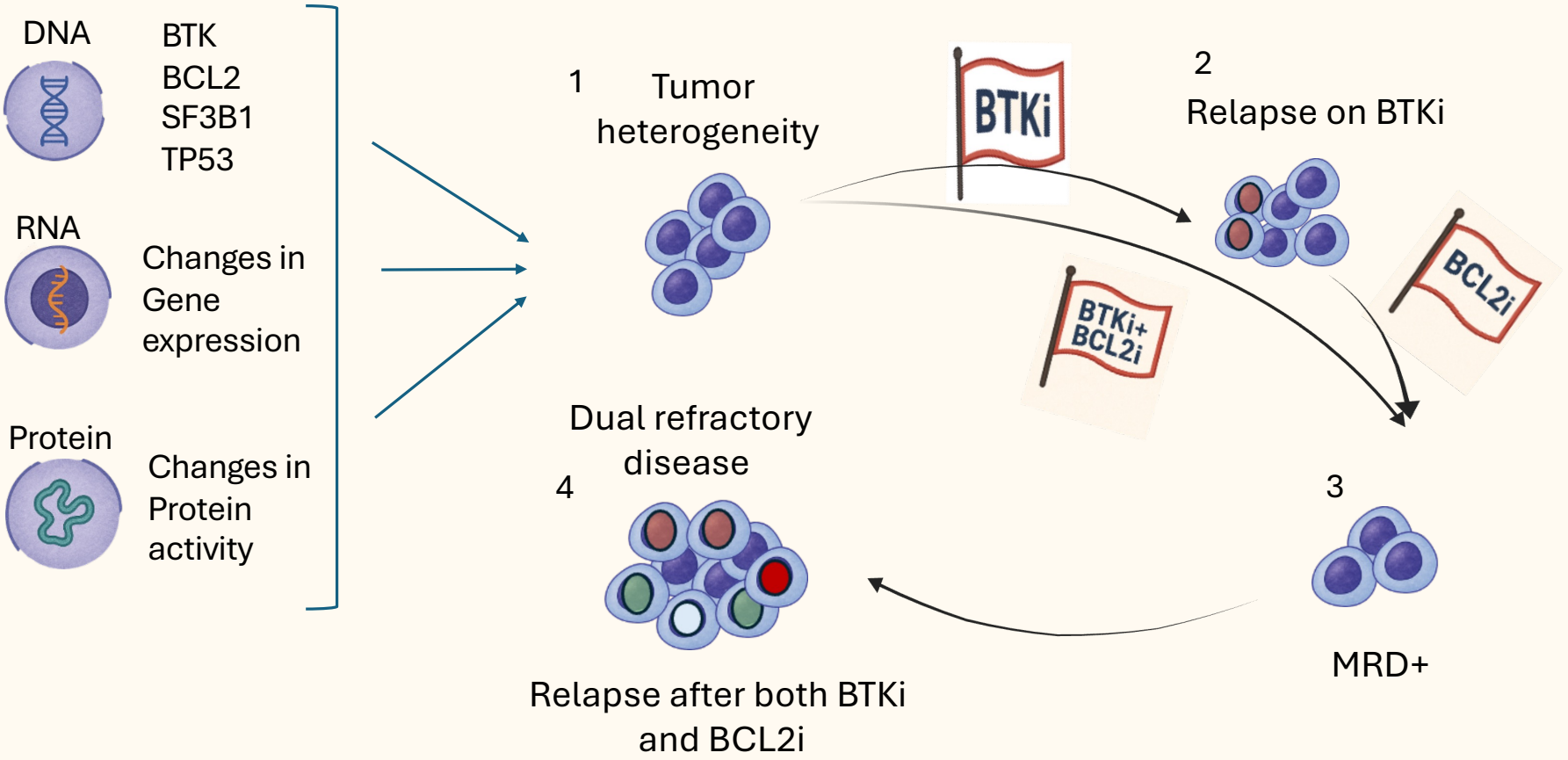
How do CLL Cells Outsmart Treatment to Return

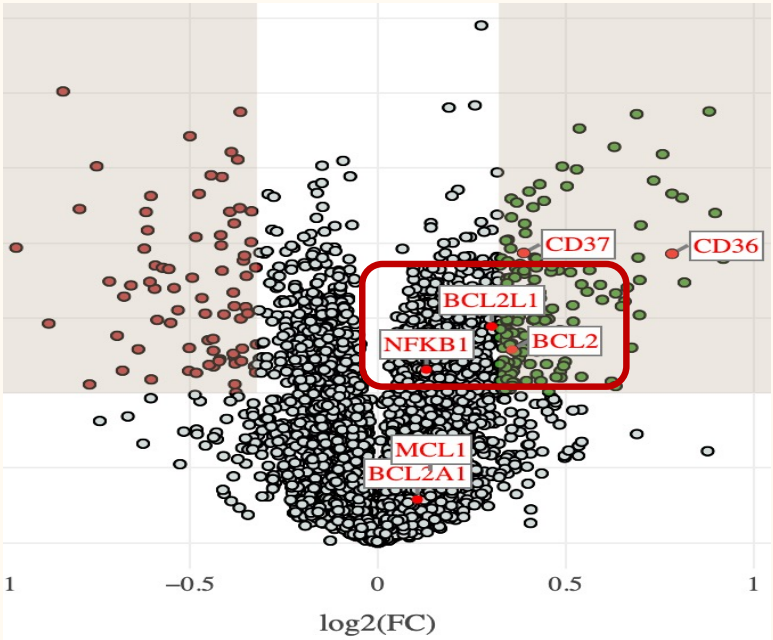


What does the DNA look like in dual refractory CLL

They re-accumulate all the different gene alterations (mutations) in BTK that drove resistance to previous BTKi treatments.

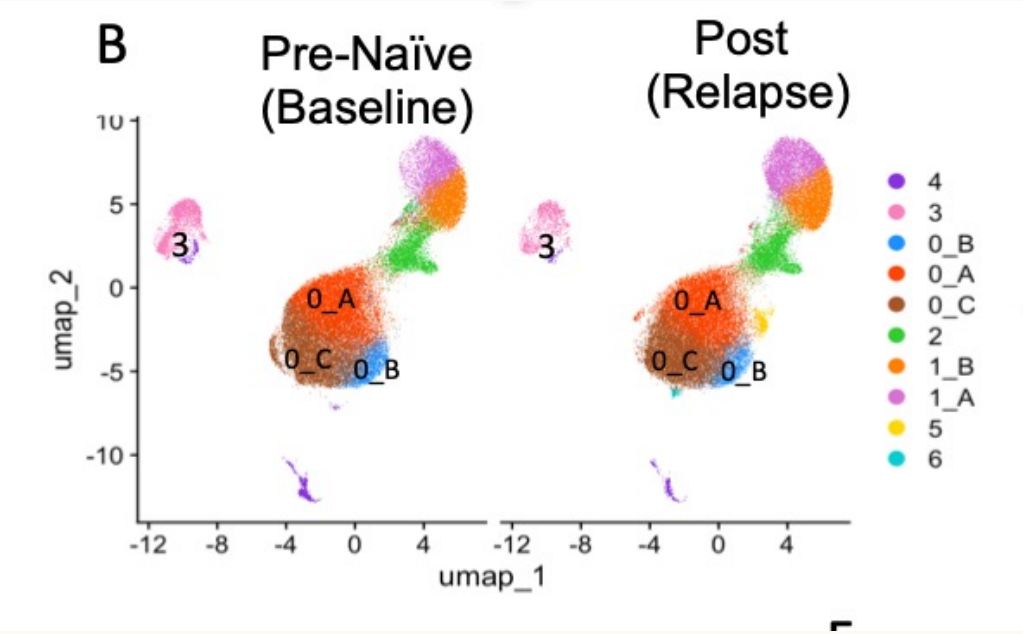
They develop gene alterations in BCL2 which causes them to resist venetoclax

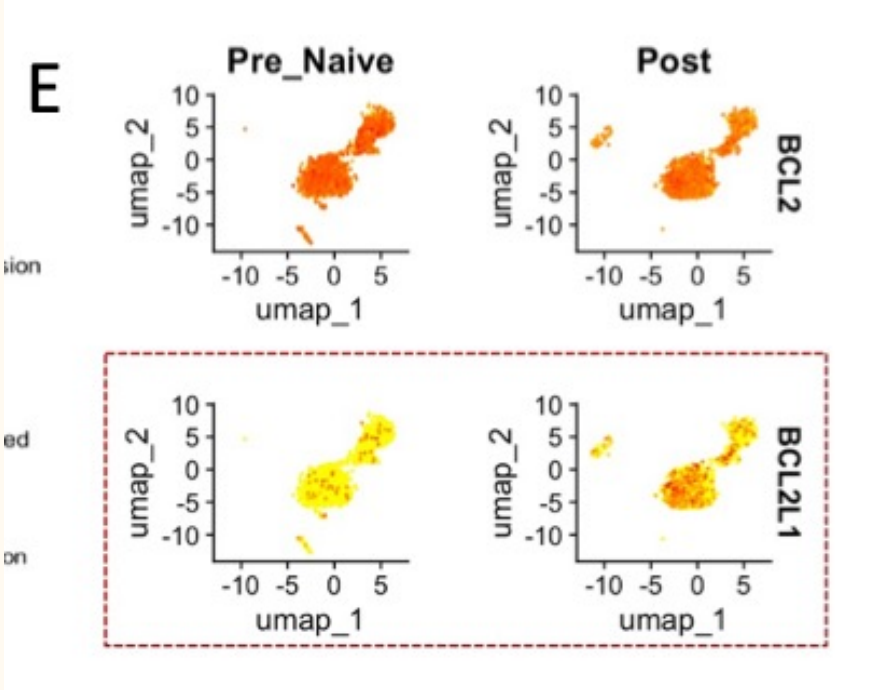
Additionally, they develop changes in other genes that increase CLL cells survival capacity



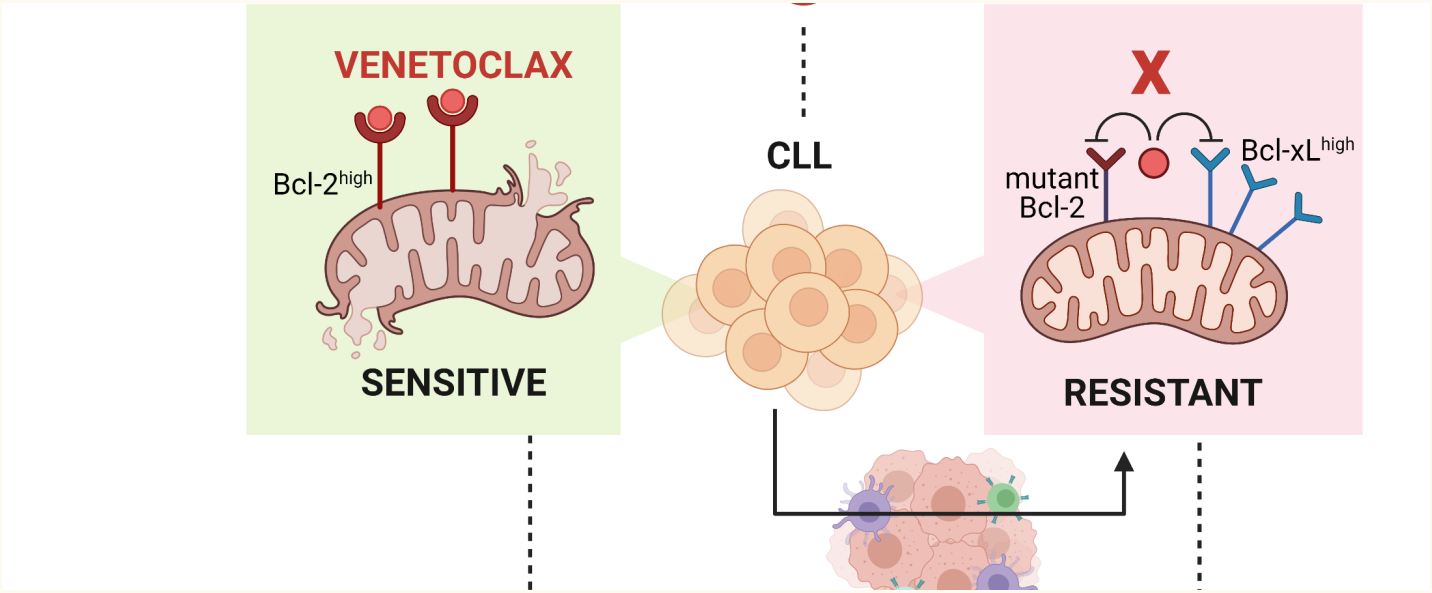
What does the RNA look like in dual refractory CLL

They change their patterns to start expressing higher levels of the BCL2 family protein BCLxL. Those cells that express BCLxL cause the tumor to regrow

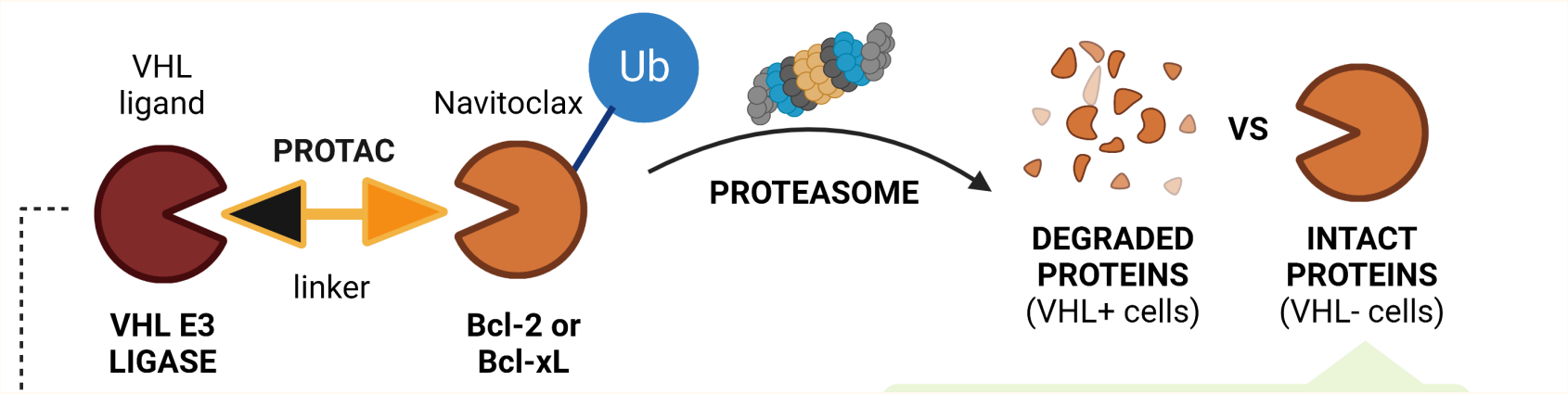




Overall, when the disease returns it now relies not only on BCl2 but on its sister proteins (such as BCLxL). If they are not eliminated the disease remains resistant to therapy



How do we fight back?



Proof of concept:

LP118 preclinical development Deepa Sampath– Newave – in Phase I trials – Nitin Jain –PI (MDACC)

- 1 CLL patient entered- promising results
- 1T-ALL patient- complete response for >1 yr

WH25244 – PROTAC degrader of BCL2/BCLxL – Preclinical development – Deepa Sampath