MECHANISMS OF ACQUIRED RESISTANCE
Cancers appear to be able to evolve resistance to many of the therapies doctors have tried. Resistance to chemotherapy likely encompasses a broad range of mechanisms having to do with DNA repair, cell cycle arrest, apoptotic pathways, and others, many of which are still unknown. When it comes to molecular-targeted agents and immunotherapies, however, research has nailed down some basic strategies.

Molecular-Targeted Therapies
- **Small molecule binding blocks intracellular signaling following the binding of a natural ligand to a receptor.**
- **Signaling pathway is activated by another means, downstream of the blocked receptor.**
- **Drug cannot target cells of a different type.**
- **Tumor cells can lose characteristics of their typical cell type and acquire characteristics of a different lineage that does not depend on signaling blocked by the cancer drug.**

Immunotherapies
- **Immune signals trigger tumor cell apoptosis.**
- **Tumor cells do not induce apoptosis.**
- **Mutations can render tumor cells less recognizable to the immune system or less responsive to molecular signals from immune cells.**
- **Mutations and other changes alter the target protein. These can include altered splicing of the tumor target, which blocks recognition by the engineered T cell.**

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**Cell type A**

**Cell type B**

**Leukemia cell**

**Engineered receptor**

**CD19**

**Engineered receptor**

**CAR T cell**

**T cell remains dormant.**

**T cell is activated to attack the tumor.**

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