Targeted drugs for Lymphoma

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The good news is that lymphoma, a blood cell cancer, is typically sensitive to standard cytotoxic chemotherapy and radiotherapy. Indeed some types of lymphoma are cured with standard treatments.

However there remains an urgent need to:

- To increase the cure rate -- and to cure more types of lymphoma
- To improve the duration and quality of responses
- To overcome treatment-resistance
- To decrease the short- and long-term toxicity of treatments overall.

Our goal is to foster understanding of how the emerging targeted agents for lymphoma are thought to work - as an aid to informed decision making.

What is a pathway?

Targeted drugs to treat cancer work in many different ways - commonly by interfering with a pathway that supports the growth or persistence of the abnormal cells.

A pathway is like a system in an automobile that controls how the vehicle works. The electrical and fuel system might be called pathways that control how a vehicle runs.

A cell pathway can be modified by a drug when it binds to the part of the cell that supports the cell activity - similar to how a mechanic must turn a specific screw to change the fuel-air mixture to modify how fast an engine runs.

The binding sites of targeted drugs may be on the cell surface or inside of the cells. Targeted drugs may also bind to normal bystander cells that promote malignant behavior -- sometimes referred to as the tumor microenvironment.

The binding of the drug to the cell part is similar to how a key will fit only one kind of lock.
The best drugs have a high **affinity** (a good fit) for the target and therefore remain engaged with the target.

Desirable **targets** for a drug are those that can interrupt or turn off a pathway that promotes the abnormal cell growth and persistence of the malignant cells.

Effective targeted drugs may also activate (turn on) pathways that help the cell to self-destruct. This would be similar to an intervention by a mechanic that turns on the breaking system allowing the automobile to stop normally.

Other targeted drugs may prevent signals from the tumor cells that shut down an attack by the immune system (immune checkpoints).

An **active drug** inhibits or activates a pathway that causes tumor cells to die.

An **effective drug** is one that is active with acceptable side effects - leading to the patient living longer and or better (clinical benefit).

The goal of early phases of clinical research is find a safe dose that shows activity against the disease. The later phases are done to see if the active dose is also effective - provides meaningful clinical benefit.

The binding sites for the drug on the cell may be highly specific to the tumor cells (not found on any other cell) or they may be expressed (turned on) in a limited type of normal cells, such as only on mature b-cells.

The higher the **specificity** and **affinity** of the drug to the tumor cells, the fewer kinds of side effects (off-target) effects there will be. However, the significance of the off-target effects also depends on the type of cells that are affected: heart cell versus skin cell, for example.

For lymphoma there are many promising targets for cancer drugs that bind to and kill only mature b-cells. A well-known example is CD20, the binding site of Rituxan, which is found only on the surface of mature b-cells. After therapy that eradicates mature b-cells, normal b-cells can emerge from the immature b-cells that the drug did not stick to.

Notably, some targeted therapies, such as antibodies, may kill lymphoma cells indirectly. Here the binding of the drug to the cell acts like a flag attracting immune cells that then kill the cells.

One reason for optimism that progress against lymphoma will continue is the number of targets that are specific to mature b-cells that can be targeted in this way; another is the high sensitivity of lymphoma cells to regular therapies.

Some targeted drugs have already proven effective in the treatment of lymphoma, such as Rituxan and Zevalin, and more recently ibrutinib for some types of lymphoma. However, testing is needed for each new agent. (That a new drug is "targeted" does not mean it will also prove to be more effective or safer than regular treatments for lymphoma).

While single and multi-drug combinations of targeted drugs may eliminate the need for chemotherapy one day, the most effective use of targeted agents may be when used with these very active and effective standard treatments.

**We at PAL urge you to consider clinical trials ... with the help of an expert who has firsthand information about your condition, history, and treatment goals.**

See PAL’s **Trial Talk** page for a list of 100 experts you might consult:

[www.lymphomation.org/trial-talk.htm](http://www.lymphomation.org/trial-talk.htm)

**PAL’s website statistics:** Unique Visitors to Lymphomation.org:

- **Jan 2015:** 64,265

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