Second-generation Proteasome Inhibitors

Current drugs

The following substances are currently in clinical trials: **MLN9708** (Millenimu Pharmaceuticals), **CEP-18770** (Cephalon & Cell Therapeutics Europe), **Carfilzomib** (Proteolix), and **NPI-0052** (Nereus Pharmaceuticals).

MLN9708

It is chemically similar to bortezomib and, like bortezomib, inhibits the 20S proteasome reversibly (after some time it is released from the site of attachment to the 20S proteasome). Unlike bortezomib, it is also effective when given orally. Four ongoing clinical trials (Phase 1-2) for this substance (multiple myeloma , solid tumors, lymphomas) can be found on the NCI website (https://www.cancer.gov/).

CEP-18770

This is another reversible 20S proteasome inhibitor (again chemically similar to bortezomib), but it can be also administered intravenously. Currently, only one clinical trial for this substance is underway (Phase 2, multiple myeloma).

Both other substances are irreversible inhibitors of the 20S proteasome and belong to completely different chemical groups: unlike bortezomib, which is derived from a combination of monoalkylboronic acid and dipeptide, carfilzomib is a combination of epoxyketone and tetrapeptide and NPI-0052 is bicyclic γ-lactam-β-lactone.

NPI-0052

It is also known as salinosporamide A and was originally isolated from a single marine bacterium. Four ongoing clinical trials (intravenous, phase 1, multiple myeloma, solid tumors, lymphomas) can be found for this substance on the NCI website.

Carfilzomib

It is being tested in eight clinical trials (intravenous, phase 1-2, lymphomas, leukemia, solid tumors), in combination with other drugs, even in stage 3 in patients with multiple myeloma. However, VELCADE (bortezomib) is still the only clinically used proteasome inhibitor.

Future drugs

20S proteasome inhibitors interfere with too many cellular processes at once. Rather, Hershko considered how to influence the degradation of specific selected proteins that are known to play a significant role in the development and progression of cancer. For such an approach, it is necessary to inhibit specific **E3 ligases** that determine the ubiquitination and degradation of these proteins.

MLN4924

It is the first such inhibitor to enter clinical trials recently and comes from Millenium Pharmaceuticals. In fact, it is not a direct inhibitor of any E3 ligase, but an **inhibitor of the NAE** (NEDD8-activating enzyme), which regulates one group of E3 ligases. In this sense, MLN4924 represents a completely unique approach to cancer treatment that has not yet been tested at all. Four clinical trials for this substance can be found on the NCI website (intravenous, phase 1, melanoma , leukemia, lymphoma, multiple myeloma and also solid tumors).

References

Related articles

- Cell degradation system
- Ubiquitination
- Deubiquitination
- Proteasome and its inhibitors
- Studies on Proteasome Inhibitors
- History of proteasome inhibitors
- Antabus

Source

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Citations

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