Proteasome inhibitors / history

The successful application of the proteasome inhibitor **bortezomib** (given as a drug called VELCADE®) against multiple myeloma is still considered incredible, for example on the website of the National Cancer Institute (https://www.cancer.gov/) (NCI), as an exemplary „success story“. No other intervention in the Ubiquitin-Proteasome System (UPS), other than the use of bortezomib, has been approved as a therapeutic approach applicable to human patients in routine clinical practice. Details of the discovery and development of bortezomib will be discussed below, based on three main sources (unless otherwise stated): an interview with *Julian Adams* for Myeloma Today (https://www.myeloma.org/?articleId=1029) (6.5.2003), and The Velcade Story in the Boston Globe (http://www.bostonglobe.com) (6.5.2007) and from the article *Velcade: First in a New Class of Cancer Drug* on the website Science Progress (Harvard Medical School) (http://scienceprogress.hms.harvard.edu/index.html).

At Harvard

As mentioned above, Hershko and his group followed the work of the group of prof. Goldberg of Harvard, who also coined the name "26S proteasome" for an entity that degrades proteins in mammalian cells in a non-lysosomal manner. Goldberg's group gradually discovered that these proteasomes are present in all eukaryotic cells and that there are tens of thousands of them in each cell. Goldberg soon realized that these findings could be of therapeutic value, for example in the treatment of muscle atrophy, which has various causes - starvation, cancer, AIDS, TBC – and results in **excessive degradation of proteasome proteins** proteazomy in muscle.

Establishment of MyoGenics

With three other Harvard professors in the field, namely T. Maniatis, M. Rosenblatt and K. Rock, Goldberg founded **MyoGenics**, in 1993 to commercialize the knowledge gained as new drugs. The first known proteasome inhibitor, named after MG132, was also prepared here. n collaboration with K. Rock, Goldberg was able to demonstrate the role that proteasomes play in the immune system and together with Maniatis's laboratory, discovered the importance of the proteasome for NF-κB activation.

Synthesis of bortezomib

náhled|200px|vpravo| Bortezomib Based on Maniatis' research, MyoGenics changed its name to **ProScript** ProScript, focusing no longer on muscle atrophy, but on the relationship between proteasomes (Pro) and transcriptional regulation (Script). At the time, Goldberg and his associates employed chemist J. Adams, who already had experience working on the development of new drugs in large pharmaceutical companies. In the fall of 1994, Adams developed a specific and very potent proteasome inhibitor called PS-341, later known as **bortezomib**. At that time, Adams, in consultation with A. Hershke and with the support of T. Maniatis, believed that ProScript must focus on the use of bortezomib in the treatment of cancer. And a year later, bortezomib was first shown to suppress cancer growth in vivo (in mice). However, Goldberg, most ProScript employees, as well as outsiders, were convinced that massive use of bortezomib in human patients would have fatal side effects and did not support **Adams' direction**.

Way to LeukoSite

A key turning point was D. Livingston's arrival on the ProScript Scientific Council, as well as Adams' collaboration with E. Sausville of NCI. The first clinical trial of bortezomib, administered intravenously as VELCADE®, was launched in October 1998 under the direction of R. Orlowski at the University of North Carolina, which also funded the entire trial. At that time, ProScript no longer had money. What happened next?

In 1997, the wealthy philanthropist W. Steinberg, whose company Health Care Ventures owned all the shares of ProScript, died. Steinberg's successors did not believe in Adams' direction, and in June 1999 they **sold ProScript** for $ 2.7 million to **LeukoSite**, which was bought three months later by Millennium Pharmaceuticals for $ 635 million. All of these stores took place within Cambridge v Massachusetts (https://www.google.com/maps/search/cambridge/data=!4m2!2m1!4b1?sa=X&dg=dbrw&newdg=1), which also houses Harvard University (and behind Charles River in Boston is Harvard Medical School and associated clinics such as the Dana-Farber Cancer Institute).

Millennium Pharmaceuticals did not purchase LeukoSites because of VELCADE®, but as a competitor involved in the development of anti-inflammatory drugs. Adams and his direction were an insignificant part of LeukoSite.

At the University of North Carolina

Meanwhile, clinical research in North Carolina has shown that bortezomib **has no serious side effects** and may have great potential for the treatment of some cancers. n 2000, R. Orlowski's team observed low-dose multiple myeloma in a 47-year-old patient using low doses of bortezomib, which are used only to verify the safety of the drug. Under these circumstances, the head of the oncology department at Millennium Pharmaceuticals, J. Bolen, already understood the importance of the further development of VELCADE®, and the management, led by M. Levin, was equally positive about Adams's efforts.

Way to promote bortezomib

náhled|200px|vpravo| Sídlo Dana-Farber Cancer Institute Adams teamed up with K. Anderson, a multiple myeloma specialist at the Dana-Farber Dana-Farber Cancer Institute (https://www.dana-farber.org/), to persuade Levin to pay the Millennium for other clinical trials. Two other factors were essential:

1. First, Adams and Anderson have partnered with patient organizations suffering from multiple myeloma. There was virtually no working therapy for this type of cancer at the time, so the interest in authorizing bortezomib for routine clinical use was huge.
2. The second key circumstance was the close cooperation between the people of Millennium Pharmaceuticals and the US Drug Enforcement Administration FDA (https://www.fda.gov/) (Food and Drug Administration).

The results of other clinical trials were so amazing that on May 13, 2003, the FDA approved bortezomib for the treatment of patients with relapsing multiple myeloma before the completion of Phase 3 clinical trials, which are usually required for such approval. In 2008, bortezomib was approved in the United States as a drug of first choice against multiple myeloma and is now used mainly in combination with other drugs.[1]. Bortezomib is indicated for the treatment of multiple myeloma commonly in Europe, Japan and elsewhere in the world. For Millennium Pharmaceuticals, this drug has become a very important source of income (according to the Boston Globe article, it is about a third of all the company's profits). In many cases, however, bortezomib is not a complete treatment for the disease, but "only" a prolongation of life by months.

Efficacy of bortezomib

According to one of the recent studies [2] out of 64 patients with multiple myeloma who took bortezomib, 9% were cured and 41% achieved at least partial suppression of the disease. The median duration of drug susceptibility was 8.4 months and the median time to disease progression was 17.3 months. There are currently hundreds of clinical trials of bortezomib against multiple myeloma and other cancers. In principle, **bortezomib has been shown to fail in cases of solid tumors**, while some blood tumors (lymphomas) re sensitive to it (details are in the table; more information on individual clinical trials can be found on PubMedu (https://www.ncbi.nlm.nih.gov/pubmed/)).

Results of clinical trials with bortezomib (without combination with other medicinal products) until 2010.

type of disease	results of clinical trials
multiple myeloma	in clinical treatment
mantle cell lymphoma	in clinical treatment
cutaneous T-cell lymphoma	significant activity in the 2nd phase of tests
MALT lymphoma	significant activity in the 2nd phase of tests
Waldenström's macroglobulinemia	significant activity in the 2nd phase of tests
chronic lymphocytic leukemia	biological activity in the 2nd phase of tests
childhood leukemia	low activity in the 1st phase of tests
soft tissue sarcomas	low activity in the 2nd phase of tests
small cell lung cancer	low activity in the 2nd phase of tests
colorectal cancer	no activity in the 2nd phase of tests
melanoma	no activity in the 2nd phase of tests
neuroendocrine tumors	no activity in the 2nd phase of tests
breast cancer	no activity in the 2nd phase of tests
non-small cell lung cancer	no activity in the 2nd phase of tests
gastric and esophageal cancer	no activity in the 2nd phase of tests

Links

Related articles

- Degradační systém buňky
- Ubikvitinace
- Deubikvitinace
- Proteazom a jeho inhibitory
- Studie zaměřené na Inhibitory proteazomu
- Inhibitory proteazomu 2. generace
- Antabus

Source

-

References

1.
2.

Kategorie:Biochemie Kategorie:Hematologie