HIV protease inhibitors that have mainly been used to treat Human Immunodeficiency Virus (HIV) infection have also shown potential as cancer treatments against certain types of cancers. This has been first verified by researchers from the National Cancer Institute, which is part of the National Institutes of Health (NIH). The most common HIV protease inhibitors are Nelfinavir (Viracept®), Ritonavir (Norvir®), and Saquinavir (Invirase®). The discovery was a result of experimentation of drugs already on the market. New drug development is very time-consuming and extremely expensive. Existing drugs have passed the majority of safety and regulatory guidelines, which makes for easier to test on patients.

A general mechanism has been proposed to show how these protease inhibitors have anti-cancer activity in non-HIV-associated human cancer cells. The underlying mechanism of the anti-tumor effect involves the stimulation of the endoplasmic reticulum stress response (ESR), which is shown by an increase of two ESR markers. The induction of ESR is important because it sensitizes the cell for cell death. There is an accumulation of misfolded proteins, which indicates proteasome inhibition. These factors lead the cell to apoptosis, or programmed cell death (removal of old or damaged cells). Nelfinavir and Saquinavir were the most potent of the HIV protease inhibitors being examined. Non-apoptopic cell death also involves the stimulation of the endoplasmic reticulm, which can lead to the a normal process of self-digestion, known as autophagy.

In one study, Nelfinavir and Saquinavir were shown to be more potent than the other HIV protease inhibitors examined. They each had similar abilities to prevent tumor growth, and induce programmed cell death, or apoptosis, which is a normal process that rids the body of old or damaged cells. The molecular structures of these two drugs share a trait that is not found in the other drugs that were tested, and the researchers speculate that this trait might provide an explanation for the relatively higher potency of these two drugs. Nelfinavir was the most effective of all the protease inhibitors tested, and was able to cause two different types of cancer cell death—apoptosis and non-apoptotic cell death. ER stress and autophagy are very important cellular processes that are currently being investigated in cancer research. Impaired autophagy (unable to recycle or destroy older cells) often leads to development of cancer.

The specific mechanism behind these HIV protease inhibitors is widely debated. The team that initiated the research found that HIV protease inhibitors were effective because they inhibited the activation of a protein referred to as Akt. This protein has been involved with the development of many types of cancer.

One research group found that Nelfinavir was effective at slowing the growth of breast cancer tumors involving the HER2 protein. HER2-positive breast cancer comprises nearly 30% of all breast cancers, and it is less responsive to traditional hormone treatments. Nelfinavir successfully inhibited growth of tumors that had become resistant to the commonly used breast cancer drugs lapatinib and trastuzumab. Further experimentation showed that Nelfinavir's mechanism of action involved the HSP90 protein, which also binds to HER2. Experimentation on pituitary adenomas by researchers showed that HIV protease inhibitors could overcome the high secretory activity and stabilize the cancer cells for radiation therapy.

Another research group found that HIV protease inhibitors were useful to sensitize drug-resistant cancer cells to chemotherapeutic agents and radiation therapy. Addtionally, they can be used as single agents on drug-resistant cancer cells. Ovarian cancer cells were treated with clinically applied Nelfinavir, which induced cell death (apoptosis). Nelfinavir was found to have changed the morphology of the ovarian cancer cells, which resulted in large vacuoles derived from the ER (stress) and induction of the unfolded protein response.

Lastly, Nelfinavir has been tested on patients with glioblastoma and oligodendroglioma, which accounts for the majority of primary brain tumors. The treatment strategies for this disease have not changed drastically for many years as it usually requires surgical intervention followed by radiotherapy. The addition of Nelfinavir can help sensitize the cancer cells to additional medications or radiation therapy, as well as inhibit the growth of the tumor. The modulation of the Akt protein can help down-regulate angiogenesis, which is often necessary for tumor growth.

Nelfinavir has been used in experimental trials to determine how much of the drug can be tolerated by cancer patients and to better understand how it behaves and reacts in the human body. The process of finding new functions for already approved drugs is called repositioning. Repositioning takes advantage of existing data on toxicity, pharmacokinetics, and potential side effects. Additionally, this process can better complement new drug development by reducing risks and costs. Nelfinavir is still undergoing experimentation as a potent anti-cancer drug or supplement. Difficulties stem from the lack of a specific molecular mechanism for the drug, as well as other side effects. However, researchers have indicated their optimism for the drug as it has a pronounced and versatile effect on various forms of cancer.

References:

Gills JJ, LoPiccolo J, Tsurutani J, Shoemaker RH, Best CJM, Abu-Asab MS, Borojerdi J, Warfel NA, Gardner ER, Danish M, Hollander MC, Kawabata S, Tsokos M, Figg WD, Steeg PS, and Dennis PA. Nelfinavir, **a lead HIV protease inhibitor, is a broad spectrum, anticancer agent that induces ER stress, autophagy and apoptosis in vitro and in vivo.** Clin Can. Res. Vol. 13, No. 17. September 1, 2007.

J. S. Shim, R. Rao, K. Beebe, L. Neckers, I. Han, R. Nahta, J. O. Liu. **Selective Inhibition of HER2-Positive Breast Cancer Cells by the HIV Protease Inhibitor Nelfinavir**. *JNCI Journal of the National Cancer Institute*, 2012; DOI: 10.1093/jnci/djs396

Joong Sup Shim, Rajini Rao, Kristin Beebe, Len Neckers, Inkyu Han, Rita Nahta, and Jun O. Liu. **Selective Inhibition of HER2-Positive Breast Cancer Cells by the HIV Protease Inhibitor Nelfinavir**. *J Natl Cancer Inst*, October 5, 2012 DOI: 10.1093/jnci/djs39

Brüning A, Burger P, Vogel M, Rahmeh M, Gingelmaiers A, Friese K, Lenhard M, Burges A. **Nelfinavir induces the unfolded protein response in ovarian cancer cells, resulting in ER vacuolization, cell cycle retardation and apoptosis**. Cancer Biol Ther. 2009 Feb;8(3):226-32. Epub 2009 Feb 3. PubMed PMID: 19106637.

Xie L, Evangelidis T, Xie L, Bourne PE. **Drug discovery using chemical systems biology: weak inhibition of multiple kinases may contribute to the anti-cancer effect of nelfinavir**. PLoS Comput Biol. 2011 Apr;7(4):e1002037. Doi: 10.1371/journal.pcbi.1002037. Epub 2011 Apr 28. PubMed PMID: 21552547; PubMed Central PMCID: PMC3084228.

Gills JJ, Lopiccolo J, Tsurutani J, Shoemaker RH, Best CJ, Abu-Asab MS, Borojerdi J, Warfel NA, Gardner ER, Danish M, Hollander MC, Kawabata S, Tsokos M, Figg WD, Steeg PS, Dennis PA. **Nelfinavir, A lead HIV protease inhibitor, is a broad-spectrum, anticancer agent that induces endoplasmic reticulum stress, autophagy, and apoptosis in vitro and in vivo.** Clin Cancer Res. 2007 Sep 1; 13(17):5183-94.

Bernstein WB, Dennis PA. **Repositioning HIV protease inhibitors as cancer therapeutics**. Curr Opin HIV AIDS. 2008 Nov; 3(6):666-75.

Clinical Trials (examples):

Study With Nelfinavir and Combined Radiochemotherapy for Glioblastoma:
http://clinicaltrials.gov/show/NCT00694837

Evaluation of Nelfinavir and Chemoradiation for Pancreatic Cancer:
http://clinicaltrials.gov/ct2/show/NCT01086332

Study With Nelfinavir and Combined Radiochemotherapy for Glioblastoma:
http://clinicaltrials.gov/show/NCT00694837