

# OPIOID GROWTH FACTOR (OGF) IN CANCER THERAPY

***A UNIQUE BIOTHERAPEUTIC  
AGENT***

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October '06

by

**MedInsight Research Institute**

# ENDORPHINS

Endorphins were discovered in 1975 by Dr. John Hughes and Dr. Hans Kosterlitz. The word Endorphin is abbreviated from '**endogenous morphine**' which means a morphine-like substance produced naturally in the body.

The body produces a number of endorphins, which have numerous functions in the body. These range from control of pain<sup>1</sup> and mood<sup>2</sup> to regulation of the immune system<sup>3</sup>, growth of cells<sup>4</sup> and angiogenesis<sup>5</sup>.

## OGF

One of these endorphins, met-enkephalin, has been studied extensively in relationship to growth – especially cancer. OGF (Opioid Growth Factor) is a name which has been given to **met-enkephalin**, in order to symbolize and emphasize its action in relation to control of growth of cells.

Professor Ian S. Zagon and a research team, at The Pennsylvania State University, the M.S. Hershey Medical Center, discovered that endogenous opioid peptides served as growth factors. In subsequent studies, these researchers found that one native opioid peptide – met-enkephalin (OGF) regulates the growth of cancer cells. They further discovered that the effect of OGF is mediated by a receptor. Originally named the  $\zeta$  (zeta) receptor because it was thought to be a new member of the opioid receptor family, recent cloning and sequencing of this receptor has demonstrated that it is not like classical opioid receptors. The receptor for OGF was renamed the Opioid Growth Factor receptor (OGFr).

Of the wide variety of cancer cells examined to date, all use the OGF-OGFr system in growth regulation. The effect of OGF is to delay the replication of cells. The retarding of cell multiplication is often referred to as cytostatic (cyto = *cellular growth*, static = *halt*). Unlike chemotherapy, OGF does not directly destroy cancer cells and is not cytotoxic. It does however halt the growth of the cells and is thought to allow immunological mechanisms (e.g. macrophages, natural killer cells) to accomplish the task of destroying the cancerous cells.

OGF also appears to work in harmony with chemotherapeutic agents. When given in combination with OGF, chemotherapy is likely to work in a more efficacious manner.

## **OGF AND ANGIOGENESIS**

Angiogenesis refers to the creation of new blood vessels. The pioneer in this field, Professor Judah Folkman of Harvard Medical School, discovered that tumors produce new blood vessels in order to enable them to obtain the nutrients which they need to grow at a rapid pace. This process is known as angiogenesis and this enables tumors to metastasize (spread) to other organs in the body. Since this discovery, billions of dollars have been invested in developing drugs which can halt this process, thus slowing the growth of tumors or starving them of the nutrient supply which they need.

OGF has been found to inhibit angiogenesis, thus adding to its role in cancer therapy, by inhibition of tumor growth and perhaps metastasis<sup>6 7</sup>.

## **IMMUNO-REGULATING PROPERTIES**

In addition to its anti-cancer effects, OGF has been found to have immuno-stimulating and immuno-regulating effects. It has been used to treat several autoimmune conditions in human subjects, including Multiple Sclerosis<sup>8</sup>, Uveitis<sup>8</sup>, Behcet's Syndrome<sup>8</sup>, and Optic Neuritis<sup>8</sup>. It has also been reportedly used to treat AIDS with very good results<sup>9 10 11 12 13</sup>. Much of this research has been carried out in the USA, Belgium, Croatia and Germany.

## **RAISING NK (NATURAL KILLER) CELL LEVELS**

NK cells are part of the "T" cell family in the lymphocytes. NK cells focus on destroying virally infected cells and cancer, but also kill bacteria, parasites and fungi. They are unique in that they have a special ability of recognizing invaders. They specialize in killing virus and cancer cells that other parts of the immune system no longer recognize, for whatever reason. Any cell that is "hiding" is vulnerable to attack by NK cells. This is routine occurrence as virus and cancer cells tend to try to "hide". When other parts of the immune system are so overwhelmed so as to slow or stop their function, NK cells are the last defense that exists.

Boosting NK cell levels is essential in helping to beat cancer. Studies have demonstrated that OGF significantly raises NK (Natural Killer) cell levels, although the mechanism by which this happens has not yet been fully clarified<sup>14 23</sup>.

## **WHICH CANCERS CAN BE TREATED WITH OGF?**

All the studies which have been carried out to date have consistently demonstrated the existence of OGF receptors in every type of malignancy which has been examined. Furthermore, there have been numerous anecdotal reports of a variety of cancers which respond to an OGF-boosting drug. Studies in animals have clearly determined that the mechanism for this response is through OGF/OGFr interaction<sup>15 16 17</sup>. It is therefore reasonable to assume that the responses to this OGF-increasing drug which have been anecdotally reported in humans, are similarly mediated via OGF receptors.

The following cancers have either been shown to have OGF receptors and/or have been anecdotally reported to respond to OGF and/or OGF-boosting mechanisms.

**Breast Cancer**<sup>18</sup>

**Cervical Cancer**<sup>21</sup>

**Colon and Rectal Cancer**<sup>18 19 20</sup>

**Gastric Cancer**<sup>18</sup>

**Glioblastoma**<sup>18</sup>

**Head and Neck**<sup>18 20</sup>

**Kaposi's Sarcoma**<sup>13</sup>

**Leukemia – Lymphocytic**<sup>21</sup>

**Liver Cancer**<sup>21</sup>

**Lymphoma – B Cell and T Cell**<sup>22 21</sup>

**Malignant Melanoma**<sup>23</sup>

**Neuroblastoma**<sup>18 24</sup>

**Ovarian Cancer**<sup>18</sup>

**Pancreatic Cancer**<sup>20</sup>

**Prostate Cancer**<sup>25 18</sup>

**Renal Cell Carcinoma**<sup>26</sup>

**Small Cell and Non-Small Cell Lung Cancer**<sup>18</sup>

**Throat Cancer**<sup>21</sup>

**Tongue Cancer**<sup>18</sup>

**Uterine Cancer**<sup>18</sup>

## DOSING

In addition to producing endorphins, the body also produces enzymes which break down endorphins. These are known as endorphinase or enkephalinase. In order to ensure a lasting effect, OGF has to be administered at regular intervals. Different dosing schedules are used depending on the estimated "tumor burden" in the body.

Clinical Research carried out at Hershey Medical Center has successfully completed Phase 1 trials and is now in the midst of Phase 2 trials. The doses used are either 250 micrograms per k.g. of bodyweight, via intravenous infusion (once or twice weekly), or 50 micrograms per k.g. of bodyweight, via subcutaneous injection (twice daily).

## Conclusion

OGF appears to be an extraordinarily promising agent in the therapy of cancer. Phase I studies have determined an excellent safety profile, which is practically unrivaled in the field of oncology therapeutics. Furthermore, OGF has been demonstrated to exert beneficial effects on the immune system, thus eliminating fears of long-term damage to the body and immunity.

Since OGF is not a patentable substance, no incentive exists for commercial sponsorship of further human studies. Rather, most of the sponsorship to date has been from governmental sources.

Commercial exploitation of the benefit of OGF is planned through the development of OGF analogues (agents which mimic its action). Such analogues are patentable and therefore provide an incentive for financial investment by pharmaceutical companies which stand to profit from future sales.

In order to benefit from OGF, it is possible to enroll in a clinical trial where available. A Phase II trial for pancreatic cancer is underway at Hershey Medical Center, PennState University. A trial for head & neck cancer will be recruiting soon. Another possibility is to obtain OGF as a compounded injectable from non-cGMP or cGMP approved suppliers.

## Availability

One source for OGF is Biofactor GMBH in Germany, where it is sold under the name LUPEX®. LUPEX® is intended for human use in cancer, AIDS and autoimmune diseases, Biofactor Tel +49 5322 96 05 14, Fax +49 5322 30 17. Their email is [info@biofactor.de](mailto:info@biofactor.de)

This is not an endorsement of this manufacturer or their product. As we were last notified, the material Biofactor use is not cGMP grade, and therefore is only suitable for subcutaneous injection, and not for intravenous infusion.

Another source for OGF is Netzah Israel Pharmacy in Tel Aviv, Israel. Their Fax number is +972-3-7617329. Their email is [pharmacy@medinisrael.com](mailto:pharmacy@medinisrael.com)

This is not an endorsement of this manufacturer or their product. As we were last notified, the material which Netzah Israel Pharmacy use is cGMP grade, and therefore it is suitable for both subcutaneous and intravenous administration.

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## REFERENCES

- <sup>1</sup> Terenius L. Endorphins and modulation of pain. *Adv Neurol* 1982; 33:59-64.
- <sup>2</sup> Olson GA, et al Endogenous opiates: 1992..*Peptides*. 1993 Nov-Dec;14(6):1339-78. Review.
- <sup>3</sup> Jankovic BD. Neuroimmunomodulation: From phenomenology to molecular evidence. *Ann NY Acad Sci* 1994;741:1-38.
- <sup>4</sup> Zagon, I.S., E. Zagon and P.J. McLaughlin. 1989. Opioids and the developing organism: A comprehensive bibliography, 1984-1988. *Neurosci. Biobehav. Rev.* 13:207-235
- <sup>5</sup> Blebea, J., J.E. Mazo, T.K. Kihara, J.-H. Vu, P.J. McLaughlin, R.G. Atnip, and I.S. Zagon. 2000. Opioid growth factor modulates angiogenesis. *J. Vascular Surg.* 32:364-373.
- <sup>6</sup> Blebea, J., J.E. Mazo, T.K. Kihara, J.-H. Vu, P.J. McLaughlin, R.G. Atnip, and I.S. Zagon. 2000. Opioid growth factor modulates angiogenesis. *J. Vascular Surg.* 32:364-373.
- <sup>7</sup> Blebea, J., J.-H. Vu, S. Assadnia, P.J. McLaughlin, R.G. Atnip, I.S. Zagon. 2002. Differential effects of vascular growth factors on arterial and venous angiogenesis. *J. Vasc. Surg.* 35:532-538.

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- <sup>8</sup> Stambuk N et al Peptid-M (LUPEX) Immunotherapy in Multiple Sclerosis, Optic Neuritis and Uveitis. *International Journal of Thymology*, 1997;Vol 5 No. 9-9; pp448-464
- <sup>9</sup> Wybran J, Plotnikoff NP, Methionine-Enkephalin, A New Lymphokine for the Treatment of ARC Patients in Plotnikoff, N.J., Murgu, A.J., Faith, R., Wybran, J. (Eds.), *Stress and Immunity*, Boca Raton: CRC Press, 1991
- <sup>10</sup> Bihari B, Plotnikoff NP. Methionine Enkephalin in the Treatment of AIDS-Related Complex. in: Plotnikoff NP, Murgu A, Faith RE, Good RA (Editors) *Cytokines Stress & Immunity*, CRC Press, Inc. Boca Raton, FL, 1999
- <sup>11</sup> Plotnikoff N, Wybran J. Methionine-enkephalin shows promise in reducing HIV in blood. *Am Fam Physician*. 1989 Sep;40(3):234
- <sup>12</sup> Plotnikoff NP, Miller GC, Nimeh N, Faith RE, Murgu AJ, Wybran J. Enkephalins and T-cell enhancement in normal volunteers and cancer patients. *Ann N Y Acad Sci*. 1987;496:608-19.
- <sup>13</sup> Wybran J, Schandene L, Van Vooren JP, Vandermoten G, Latinne D, Sonnet J, De Bruyere M, Taelman H, Plotnikoff NP. Immunologic properties of methionine-enkephalin, and therapeutic implications in AIDS, ARC, and cancer. *Ann N Y Acad Sci*. 1987;496:108-14.
- <sup>14</sup> Plotnikoff NP. Opioids: immunomodulators. A proposed role in cancer and aging. *Ann NY Acad Sci* 1988;521:312-22
- <sup>15</sup> Hytrek SD, McLaughlin PJ, Lang CM, Zagon IS. Inhibition of human colon cancer by intermittent opioid receptor blockade with naltrexone. *Cancer Lett*. 1996 Mar 29;101(2):159-64.
- <sup>16</sup> Zagon IS, McLaughlin PJ. Duration of opiate receptor blockade determines tumorigenic response in mice with neuroblastoma: a role for endogenous opioid systems in cancer. *Life Sci*. 1984 Jul 23;35(4):409-16.
- <sup>17</sup> McLaughlin PJ, Zagon IS. Modulation of human neuroblastoma transplanted into nude mice by endogenous opioid systems. *Life Sci*. 1987 Sep 21;41(12):1465-72.
- <sup>18</sup> Zagon IS, McLaughlin PJ, Goodman SR, Rhodes RE. Opioid receptors and endogenous opioids in diverse human and animal cancers. *J Natl Cancer Inst*. 1987 Nov;79(5):1059-65
- <sup>19</sup> Zagon IS, Hytrek SD, Lang CM, Smith JP, McGarrity TJ, Wu Y, McLaughlin PJ. Opioid growth factor ([Met<sup>5</sup>]enkephalin) prevents the incidence and retards the growth of human colon cancer. *Am J Physiol*. 1996 Sep;271(3 Pt 2):R780-6.
- <sup>20</sup> Zagon IS, Roesener CD, Verderame MF, Ohlsson-Wilhelm BM, Levin RJ, McLaughlin PJ. *Int J Oncol*. 2000 Nov;17(5):1053-61. Opioid growth factor regulates the cell cycle of human neoplasias.
- <sup>21</sup> Anecdotal reports of clinical experience from Professor Bernard Bihari, State University of New York, Health Science Center at Brooklyn
- <sup>22</sup> Heagy W, Teng E, Lopez P, Finberg RW. Enkephalin receptors and receptor-mediated signal transduction in cultured human lymphocytes. *Cell Immunol*. 1999 Jan 10;191(1):34-48.
- <sup>23</sup> Faith RE, Murgu AJ. Inhibition of pulmonary metastases and enhancement of natural killer cell activity by methionine-enkephalin. *Brain Behav Immun*. 1988 Jun;2(2):114-22.
- <sup>24</sup> Zagon IS, McLaughlin P. Endogenous opioids and the growth regulation of a neural tumor. *Life Sci*. 1988;43(16):1313-8.
- <sup>25</sup> Kampa M, Bakogeorgou E, Hatzoglou A, Damianaki A, Martin PM, Castanas E. Opioid alkaloids and casomorphin peptides decrease the proliferation of prostatic cancer cell lines (LNCaP, PC3 and DU145) through a partial interaction with opioid receptors. *Eur J Pharmacol*. 1997 Sep 24;335(2-3):255-65.
- <sup>26</sup> Bisignani GJ, McLaughlin PJ, Ordille SD, Beltz MS, Jarowenko MV, Zagon IS. Human renal cell cancer proliferation in tissue culture is tonically inhibited by opioid growth factor. *J Urol*. 1999 Dec;162(6):2186-91.