Prostate of mind

By Lev Osherovich, Senior Writer

Neuropeptide hormones associated with pleasure and analgesia may have an unexpected role in fighting prostate cancer, according to a report in the *Proceedings of the National Academy of Sciences*.¹ The study ties together a mechanism that involves stress response, immunity and tumor growth, and it also identifies new points of therapeutic intervention. Industry researchers were intrigued by the findings, but cautioned that clinical applications are a long way off.

Dipak Sarkar, professor of animal sciences at **Rutgers University** and team leader on the *PNAS* paper, told *SciBX* that the study stems from his long-standing interest in how β -endorphin (BEP) influences brain development, immunity and cancer. BEP is a small peptide hormone made in the hypothalamus by the cleavage of proopiomelanocortin (POMC), a precursor to a number of neuropeptide hormones. BEP is secreted during stress, exercise and sex, activating opioid receptors in the nervous system to relieve pain and boost vascular function.²

Low BEP levels have been implicated in seemingly unrelated, non-neurological diseases. “Patients with schizophrenia or depression have low BEP and a higher incidence of infection and cancer,” said Sarkar. The team hypothesized that raising BEP activity might have the opposite effect and prevent tumor growth.

Because BEP is short-lived and precisely localized *in vivo*, it has been difficult to administer the peptide directly into the small part of the brain that actually responds to the hormone, according to Sarkar. To get around that problem, his team developed a cell-based delivery method to raise BEP levels in rats.

The researchers first exposed cultured neuronal stem cells to a pituitary gland-derived peptide that triggered the cells to differentiate into BEP-producing neurons, and then the researchers implanted them into the hypothalamus. After confirming that the implanted BEP neurons could survive and produce extra BEP in rat brains, the team asked whether the cells boosted immunity.

Indeed, rats with extra BEP neurons showed higher plasma levels of the anti-inflammatory cytokine interferon- γ (IFN- γ) and lower levels of the proinflammatory cytokine tumor necrosis factor- α (TNF- α) than untreated controls, suggesting less susceptibility to inflammation.

Moreover, BEP cell recipients had higher levels of NK cell activity than mock-treated controls. NK cells are part of the innate immune

system, which is the first line of defense against infection and cancer.³

“We thus created a situation where the basal level of NK cell activity is elevated,” said Sarkar. “This let us test the hypothesis about cancer.”

Implanted BEP neurons protected rats from prostate cancer, the researchers found. When exposed to a carcinogenic agent together with testosterone, mock-treated rats developed hyperplastic and neoplastic prostate tumors, whereas rats with extra BEP neurons did not.

Mind-body connection

Sarkar told *SciBX* that the main novelty of the study lies in the technique of making BEP neurons in cell culture and the finding that extra BEP antagonized tumor development. He thinks the connection between BEP and cancer development is mediated through the innate immune system, in line with previous studies.⁴

The precise mechanism of how BEP activates innate immunity has yet to be worked out. Nevertheless, the study offers therapeutic entry

points into immunity and cancer for companies developing technologies to modulate neuropeptide signaling.

“I have to say it’s a real surprise,” said Michael Cowley, CSO of **Orexigen Therapeutics Inc.** “There have been hints of this activity before, but this is the most robust demonstration of the role of POMC on cancer cells yet.”

Orexigen focuses on targeting POMC production in the hypothalamus to treat obesity and behavioral disorders. The company’s Contrave, a combination of naltrexone and bupropion, is in Phase III trials for obesity.

Palatin Technologies Inc. president and CEO Carl Spana told *SciBX* that the key new result of Sarkar’s study is that cultured neural stem cells could be made to differentiate into BEP-producing neurons that remained functional when implanted. However, the technical challenges of neural implantation mean that “for human application there is a long way to go.”

Spana also noted that the cell culture and implantation techniques used by Sarkar’s team to promote BEP cell growth would be hard to replicate in humans.

Palatin is developing compounds to modulate downstream targets of POMC-derived neuropeptides to treat obesity and hypertension. Palatin’s PL-3394 atrial natriuretic peptide receptor agonist is in Phase IIa trials to treat hypertension.

Another challenge to therapeutic application of BEP is the precise localization needed to elicit the correct effects.

“This article is exciting from our perspective as it shows that biological factors delivered locally within the brain can have significant therapeutic potential,” said Lars Wahlberg, EVP and COO of **NsGene A/S**. The Danish company is developing implantable devices to deliver therapeutics to the brain.

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NsGene's NsG0202 implantable encapsulated cell (EC) biodelivery device, which delivers nerve growth factor (NGF), is in Phase Ib trials to treat Alzheimer's disease (AD).

Wahlberg told *SciBX* that NsGene's EC biodelivery device could be "implanted in the relevant areas" of the hypothalamus, and, unlike the cellular implantation technique used in the study, is reversible.

An additional question is whether BEP is the sole POMC-derived peptide responsible for the anticancer effects of implanted BEP cells.

"Adrenocorticotrophic hormone and α -melanocyte-stimulating hormone are also produced from POMC and are known to have potent effects" on immunity and potentially directly on NK cells, said Spana.

"The POMC molecule is sort of promiscuous," said Cowley. Sarkar's study "doesn't rule [out] the other peptides as antineoplastic agents."

If other peptides derived from POMC are involved, it may be possible to mimic their effects on innate immunity and tumors using agonists of downstream receptors.

"Whether BEP is sufficient or not, I don't know," said Sarkar. "But the BEP cells are necessary" for the beneficial effects.

Spana also noted that Sarkar's experiments showed that BEP cells protected against the induction of prostate cancer by carcinogens, but did not

address whether the cells could fight pre-existing tumors.

The next step, Sarkar said, is to test whether boosting BEP production can protect against other forms of illness known to be affected by innate immunity, such as infection and inflammation. "The prostate is just a start," he said.

Sarkar said that he was "interested in contacting companies" to develop the BEP cell implantation technology, which is the subject of a pending patent that is available for licensing from Rutgers.

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COMPANIES AND INSTITUTIONS MENTIONED

NsGene A/S, Ballerup, Denmark

Orexigen Therapeutics Inc. (NASDAQ:OREX), San Diego, Calif.

Palatin Technologies Inc. (AMEX:PTN), Princeton, N.J.

Rutgers University, New Brunswick, N.J.