

## A PAPER CUT THAT COULD CAUSE CANCER

Vaibhav Mokashi



It is widely known that chronic wounding or burn sites on the skin have been associated with tumours such as the Marjolin's ulcer or "kangri cancer". However, the possibility of mutated cells migrating to the skin's surface and causing cancer was not considered.<sup>1</sup>

Wong and Reiter studied a mouse model for basal cell carcinoma, a common type of skin cancer that is associated with mutations in an oncogene called Smoothed one. In a batch of mice, the mutated oncogene was activated but this alone did not increase the rate of cancer. However, in the second group, the mutated oncogene was activated and then a wound the size of a paper cut was made by removing a small piece of skin from the mice's back. Wong and Reiter found that in the second batch of mice, stem cells with the mutated genes remained near the follicles in the lower layer of skin until the mice were wounded. Once injured, the mutated stem cells migrated to the upper layers in an attempt to fix the damage. Due to the mutation, the stem cells actually activated a biochemical pathway associated with carcinoma rather than healing the tiny wound.<sup>2</sup>

In conclusion, the study provides evidence in favour of an important principle: movement of cells with oncogenic mutations to sites that are susceptible to cancer can lead to tumour formation.<sup>1</sup>

## THE ROLE OF RHO-KINASE SIGNALLING IN OBESITY

Shelly Chopra



Obesity is characterized by a dependence on excessive consumption to fulfill one's daily needs. This dependence has been attributed to a variety of factors that range from low testosterone levels to a reduced neural sensitivity to the taste of food. In a recent study, Hara et al. investigated another propagating factor in obesity: activation of the Rho to Rho-kinase signalling pathway.<sup>1</sup> Excess energy is stored in lipid form in adipocytes, fat cells, in the body. A distinct property of adipocytes is their ability to stretch to contain greater quantities of fat. This expansion, known as hypertrophy, causes structural changes and activates inflammatory signalling pathways—both of which contribute to weight gain.

Rho-kinase signalling regulates vascular smooth muscle contraction and has been shown to activate during mechanical stress in the cardiovascular system.<sup>2</sup> As adipocytes also undergo physical stress, Hara et al. hypothesized that Rho-kinase signalling is activated during hypertrophy and thus participates in the progression of obesity. In the study, mice on a high-fat diet developed significantly larger adipocytes in comparison to mice on a low-fat diet. This hypertrophy led to greater lipid storage, inflammation, and stress fibre formation. Treatment with fasudil, a Rho-kinase inhibitor, resulted in decreased weight gain, demonstrating the role of Rho-kinase signalling in fat accumulation. This finding was confirmed in subsequent in vitro cultures where manual stretching of adipocytes up-regulated Rho-kinase activity.

The study suggests that activation of the Rho-Rho-kinase pathway stimulates increased lipid storage and thus contributes to the development of obesity. Further research on Rho-kinase inhibitors, such as fasudil, may elucidate their potential as therapeutic agents in overcoming obesity.

<sup>1</sup>Hayden E. Mutant stem cells can cause skin cancer at cuts. Nature News [Internet]. 14 February 2011. Available from: <http://www.nature.com/news/2011/110214/full/news.2011.91.html>.

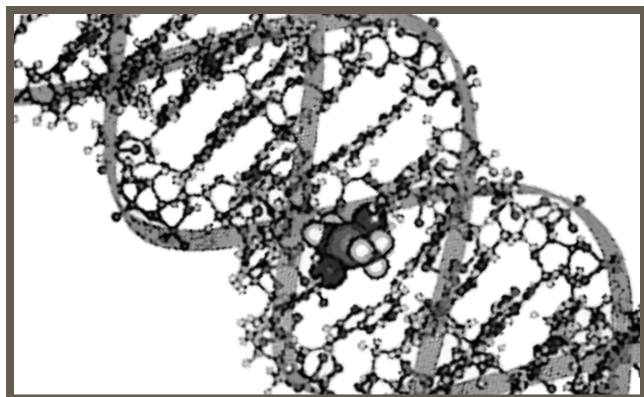
<sup>2</sup>Wong SY, Reiter JF. Wounding mobilizes hair follicle stem cells to form tumors. Proc. Natl Acad. Sci. USA 2011; doi: 10.1078/pnas.1013098108.

<sup>1</sup>Hara Y, Wakino S, Tanabe Y, Saito M, Tokuyama H, Washida N, et al. Rho and Rho-Kinase Activity in Adipocytes Contributes to a Vicious Cycle in Obesity That May Involve Mechanical Stretch. Sci Signal 2011 January 25; 4(157):3.

<sup>2</sup>Numaguchi K, Eguchi S, Yamakawa T, Motley ED, Inagami T. Mechanotransduction of rat aortic vascular smooth muscle cells requires RhoA and intact actin filaments. Circ Res 1999; 85(1):5-11.

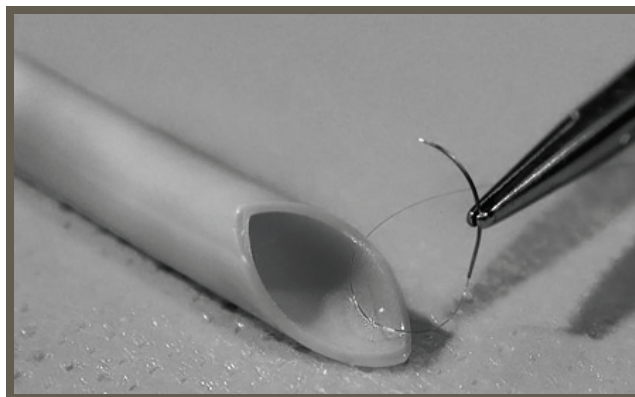
# HOOGSTEEN BASE PAIRING IN GENE THERAPY

Charles Yin



# BIOTECHNOLOGY: BLOOD VESSEL SYNTHESIS

Vaibhav Mokashi



A recent study conducted by researchers at the University of Michigan and University of California, Irvine reported the discovery of an alternate functional form of DNA.<sup>1</sup> Hoogsteen base pairing was found to occur in actively transcribing DNA 1% of the time, inducing a change in its structure.<sup>1</sup>

Hoogsteen base pairing was discovered by German chemist Karst Hoogsteen in 1963.<sup>2</sup> Hoogsteen observed that in a solution of heated adenine and thymine, a different nitrogen atom is utilized by adenine as its hydrogen bond acceptor.<sup>2</sup> An implication of this discovery is the possibility of triplex or even quadruplex DNA helices, since each base could form hydrogen bonds to two other complementary bases. Previously, this phenomenon has only been observed in RNA and damaged DNA.<sup>1</sup>

The formation of a triple helix has interesting implications for the treatment of genetic disease. Several studies have investigated the potential of using a triplex-forming oligonucleotide (TFO) in anti-gene silencing.<sup>3</sup> The binding of TFO's interferes with transcription factor binding and the formation of initiation complexes, down-regulating gene expression. There is also interest in transcription-TFO duplexes that can potentially be used to up-regulate expression of genes normally depressed in disease.<sup>3</sup>

The discovery of Hoogsteen base pairing in functional DNA is an indicator that anti-gene therapy holds considerable promise in the treatment of genetic disease.

Patients with arterial diseases are usually treated with bypass surgeries in which blood vessels which have narrowed are closed off and an alternative route for blood flow is provided by implanting another vessel. However, harvesting another compatible blood vessel can be difficult. The best alternative so far involves using the patient's own cells to develop vessels but these take up to 9 months to grow and cost over \$15000.<sup>1</sup>

Shannon Dahl, cofounder of the biotechnology firm, Humacyte, has developed a novel technique for bioengineering veins from donor cells. Donor cells are placed into scaffolds of polyglycolic acid and grown in a bioreactor. Once grown, cellular material attached to the blood vessels is removed using special detergents resulting in collagen tubes that are unlikely to be rejected by the patient's immune system. This technique allows 37 large or 74 smaller artificial blood vessels to be developed per donor in a shorter period of time. Also, because the technology does not depend on the patient's own cells, a large bank of vessels can be developed and used on demand.<sup>2</sup>

Furthermore, the durability of these blood vessels has been tested and proven on animal models. When the vessels were transplanted into baboons, they continued to function 6 months after implantation. The vessels were also successfully implanted in dogs, however, the dogs' own endothelial cells were required when it came to developing very small blood vessels.<sup>2</sup>

In conclusion, Dahl's artificial blood vessels may become extremely useful in bypass surgeries that require larger blood vessels once their long term stability is confirmed.<sup>2</sup>

<sup>1</sup>Nikolova EN, Euane K, Wise AA, O'Brien PJ, Andricioaei I, Al-Hashimi HM. Transient Hoogsteen base pairs in canonical duplex DNA. *Nature* 2011; doi:10.1038/nature09775.

<sup>2</sup>Nelson DL and Cox MM. *Lehninger Principles of Biochemistry*. 4th ed. New York: W.H. Freeman; 2004.

<sup>3</sup>Hélène C. The anti-gene strategy: control of gene expression by triplex-forming-oligonucleotides. *Anti-cancer Drug Design* 1991; 6(6): 569-584.

<sup>1</sup>O'Callaghan T. Options for off-the-shelf blood vessels expand. *Nature News* [Internet]. 2 February 2011. Available from: <http://www.nature.com/news/2011/110202/full/news.2011.66.html>.

<sup>2</sup>Dahl S. et al. Readily Available Tissue-Engineered Vascular Grafts. *Science Translational Medicine* 2011; 3(68):68ra9.

## HERBAL MEDICINE REDUCES CHEMO TOXICITY

Shelly Chopra



While chemotherapy has undoubtedly helped millions of cancer patients overcome their condition, the side effects of anticancer drugs often pose a hindrance to a patient's quality of life during the treatment period. In a recent study, Lam et al. tested the effects of PHY906, a herbal medicine extract, on the reduction of gastrointestinal irritation produced by DNA topoisomerase inhibitor, irinotecan.<sup>1</sup> This inhibitor, involved in the treatment of colon cancer, is responsible for minor side effects such as diarrhea and nausea, as well as more severe effects such as intestinal bleeding.

Unlike many other drugs that target chemotherapy toxicity, PHY906 has been found highly effective in relieving gastrointestinal malfunction. Lam et al. tested PHY906 on tumor-bearing mice that were also administered irinotecan. Researchers found that PHY906's positive effects were not limited to the regeneration of cells harmed by irinotecan. The herbal mixture also improved irinotecan's inhibitory action in reducing tumor growth and prevented rapid decreases in body weight, another side effect of the cancer treatment.<sup>1</sup>

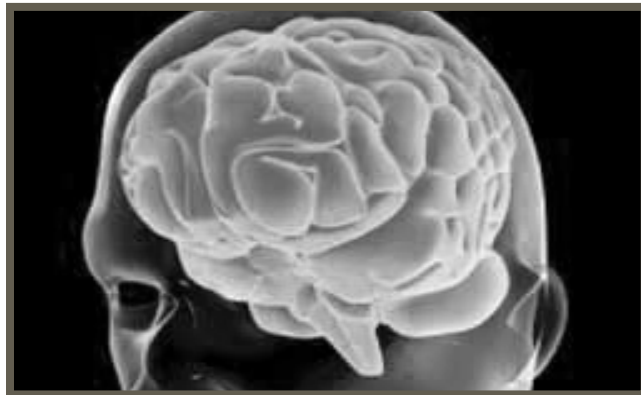
Lam et al. also investigated the mechanism by which PHY906 attenuated the inflammation caused by irinotecan. Decreased infiltration of neutrophils and macrophages—key cells involved in inflammatory responses—was found in the intestines of PHY906 treated rats.<sup>1</sup> Furthermore, PHY906 inhibited the effects of secondary messengers necessary for the onset of inflammation.

In a period of incessant biomedical advancement where pharmacological research has taken precedence over traditional remedies, this study evidences the potential of natural substances in counteracting chemotherapeutic drug toxicity.

<sup>1</sup>Lam W, Busson S, Guan F, Jiang Z, Zhang W, Gullen EA, et al. (2010). The four-herb Chinese medicine PHY906 reduces chemotherapy-induced gastrointestinal toxicity. *Science translational medicine*, 2(45). Available from: <http://stm.sciencemag.org/content/2/45/45ra59.abstract>. [Accessed 29 October 2010].

## INDUCTION OF DEPRESSION THROUGH INFLAMMATION

Charles Yin



In recent years, researchers in the fields of immunology and psychiatry have begun to notice a startling trend: patients with chronic inflammatory disorders reported being afflicted with depression, bipolar disorder, and other psychiatric conditions in abnormally high numbers.<sup>1</sup>

In 2009, O'Connor et al.<sup>2</sup> described the absence of depressive behavior in response to severe bacterial infection in mice deficient in a critical cytokine (signaling molecules used by the immune system to mediate immune response). This cytokine was also found to be expressed at greater levels in mice that do suffer from depression. It was a connection that nobody expected. It is difficult to envision that the immune system could play such a critical role in the maintenance of the nervous system, but connections like this one may be more common than researchers previously expected. In fact, a recent discovery found that patients with chronic depression who are unresponsive to traditional anti-depressants exhibit higher levels of inflammation. The inhibition of cytokines associated with inflammation was observed to help alleviate depressive symptoms in these patients.<sup>1</sup>

The discovery of such links has generated renewed public interest in an interdisciplinary field of study, aptly if unimaginatively, named 'psychoneuroimmunology'. Dr. Andrew Miller, professor of psychiatry and behavioural sciences at Emory University School of Medicine, is optimistic about the future of this field. According to Miller, there are still a lot of unknowns in the nervous system and psychoneuroimmunology may hold the key in shedding some light into those dark corners of the human brain.<sup>1</sup>

<sup>1</sup>Harmon K. (2010). Some depression might have roots in immune-generated inflammation. *Scientific American*. Available at: <http://www.scientificamerican.com/blog/post.cfm?id=some-depression-might-have-roots-in-2010-10-28> [Accessed October 31, 2010].

<sup>2</sup>O'Connor JC et al. (2009). Interferon- $\gamma$  and tumor necrosis factor- $\alpha$  mediate the upregulations of indoleamine 2,3-dioxygenase and the induction of depressive-like behaviour in mice in response to *Bacillus Calmette-Guerin*. *J of Neurosci*, 29(13), 4200-9. Available at: <http://www.jneurosci.org/cgi/reprint/29/13/4200> [Accessed October 31, 2010].

## TRADITIONAL REHAB GETS THE LAST LAUGH

Hiten Naik



The field of rehabilitation therapy has been transformed with the advent of new technologies such as radiation-based treatments. But are these therapies actually superior to tried-and-true methods?

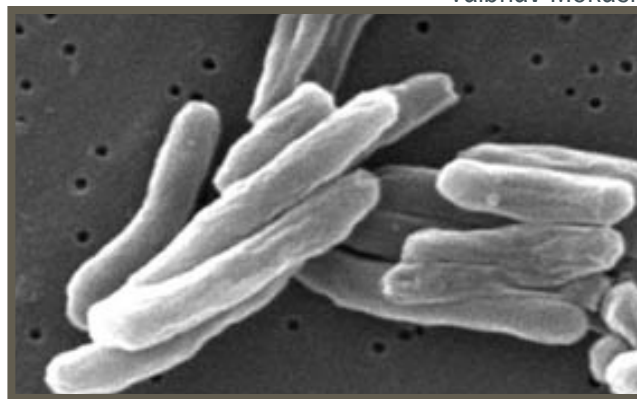
A team of researchers at Leeds University conducted a study which looked at the use of low dose ultrasound to treat leg ulcers. The ultrasound approach has become a popular rehabilitation strategy in many hospitals and the authors sought to determine if it was as effective as traditional protocols. A total of 337 patients with leg ulcers were studied for 12 weeks each. Patients that received ultrasound in addition to dressings and compression therapy were compared to those that only received standard care.<sup>1</sup>

After five years of research, the results of the study were somewhat surprising. It was found that the ultrasound technology did not the speed of healing, prevent the ulcers from returning or even improve quality of life of rehabilitating patients.<sup>1</sup> Instead, the most effective means to aid healing was through promotion of a good diet and exercise.<sup>1</sup> The authors commented that what ultimately aids in ulcer healing is the increased flow of blood up the legs and to the heart. Thus, according to lead researcher Dr. Andrea Nelson, a “really healthy chuckle” can help aid the process, as laughing causes increased diaphragm activity which in turn potentiates the flow of blood throughout the body.<sup>2</sup>

Indeed, laughter sometimes is the best medicine.

## A NOVEL NANO-THERAPY FOR TUBERCULOSIS

Vaibhav Mokashi



Tuberculosis (TB) is caused by inhalation of airborne particles containing *Mycobacterium tuberculosis*, which subsequently infiltrate the immune system to give rise to a productive cough, fever and lethargy. Antibiotics against TB have become ineffective due to the emergence of multiple strains of drug resistant *M. tuberculosis*. Consequently, a novel therapy is being developed that involves oral or aerosol administration of antibiotics encapsulated in nanobeads.<sup>1</sup>

Nanobeads consist of a polymer membrane that protects commonly used anti-TB drugs such as isoniazid and rifampin. Once nanobeads enter the body, they are actively transported across the epithelial layer of the lungs and are taken up by macrophages, the cells principally infected with and harboring *M. tuberculosis*. Macrophages engulf nanobeads through phagocytosis. The nanobeads then enter a phagolysosome, a digestive organelle within macrophages. The acidic environment of the phagolysosome catalyzes the breakdown of the polymer coating the nanobeads, thus releasing active drug to combat invading bacteria.<sup>1</sup> Interestingly, animal trials found that three oral doses of nanotherapy were as effective as 45 doses of traditionally administered antibiotic treatments.<sup>1</sup> Based on these results, this new technology may greatly reduce the dosing frequency for patients, as well as the possibility of reoccurrence due to drug resistance. Furthermore, since the nanotherapy mainly targets infected cells, it enables administration of more toxic drugs without significant damage to healthy cells. Moreover, nanobead encapsulation does not decrease the shelf life or efficacy of antibiotics.<sup>1</sup> Overall, this newfound nanotherapy has the potential to revolutionize treatment for TB, a disease that claims 1.8 million lives a year.

<sup>1</sup>Watson, JM, Kang'omb, AR, Soares, MO, Chuang, LH, Worthy, G., Bland, JM., Iglesias, C., Cullum, N., Torgerson, D., Nelson, EA. Use of weekly, low dose, high frequency ultrasound for hard to heal venous leg ulcers: the VenUS III randomized controlled trial. BMJ. 2011.

<sup>2</sup>BBC News. Laughing 'better than latest technology for leg ulcers' [online] Available at: <http://www.bbc.co.uk/news/health-12699016>.

<sup>1</sup>Griffiths G, Nyström B, Sable SB, & Khuller GK. (2010). Nanobead-based interventions for the treatment and prevention of tuberculosis. Nature Reviews Microbiology, 8, 827-834. Available from: doi:10.1038/nrmicro2437 [Accessed 23rd October 2010].