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Vaibhav Mokashi
McMaster University

Charles Yin
McMaster University

Vaibhav Mokashi
McMaster University

Shelly Chopra
McMaster University

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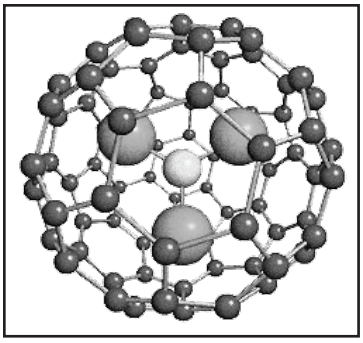
Novel Tuberculosis Treatment:
A Nano-Therapy for a Massive Disease

by Vaibhav Mokashi

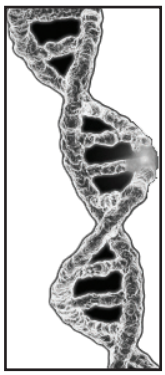


Tuberculosis (TB) is caused by inhalation of airborne particles containing *Mycobacterium tuberculosis*, which subsequently infiltrate the immune system to give rise to a productive cough, fever and lethargy. Antibiotics against TB have become ineffective due to the emergence of multiple strains of drug resistant *M. tuberculosis*. Consequently, a novel therapy is being developed that involves oral or aerosol administration of antibiotics encapsulated in nanobeads.[1] 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.[1] Interestingly, animal trials found that three oral doses of nanotherapy were as effective as 45 doses of traditionally administered antibiotic treatments.[1] 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.[1] Overall, this newfound nanotherapy has the potential to revolutionize treatment for TB, a disease that claims 1.8 million lives a year.

[1]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].

The Link between *de novo* Mutations and Sporadic Disease

by Charles Yin



When one thinks of genetic disease, the image that most often comes to mind is a condition present in the parents and then passed on to the offspring. However, >97% of cases of genetic disease are sporadic: the mutations responsible are not present in the somatic cells of either parent, but arise during germ cell replication.[1] Sporadic diseases are thought to be caused by either nondisjunction or de novo mutations in the sperm or egg cells. *De novo* mutations are novel mutations that arise naturally due to DNA replication errors. When these occur in the germ line, the mutation can be passed to offspring and a new mutation is created that can result in disease.[1] Examples of the effects of *de novo* mutagenesis are numerous. Certain forms of Parkinson's disease are sporadic and have recently been demonstrated to be the result of de novo mutations. [2] Some forms of childhood epilepsy are also the result of *de novo* mutations. A small number of disorders that constitute a subset of sporadic childhood epilepsy have been found to be the result of just a single mutation in the gamete of the parent.[3]

Now that the connection between de novo mutagenesis and sporadic disease has been clearly established, future research in this field will likely focus on the timing and location of the appearance of these mutations in the germ line. In a recent study published by Vadlamudi et al., the timing of *de novo* mutations turns out to be a critical factor in the occurrence of Dravet's syndrome (a form of sporadic epilepsy) in twins.[4] If a mutation occurs in a gamete, its chances of successfully undergoing fertilization will be dramatically decreased. However, if the mutation occurs in the germ line progenitor instead, every gamete produced will carry that mutation and every offspring produced will be affected.

[1]Lupski JR. (2007). Genomic arrangements and sporadic disease. Nature Genetics, 39, S43-7. Available at: http://www.nature.com/ng/journal/v39/n7s/full/ng2084.html [Accessed October 26, 2010]
[2]Berry AL, & Foltynie T. (2010). Gene therapy: A viable therapeutic technique for Parkinson's disease? J Neurol. Available at: http://www.springerlink.com/content/484064jjwj283863/fulltext.pdf [Accessed October 26, 2010]
[3]Stafstrom CE. (2009). Severe epilepsy syndromes of early childhood: The link between genetics and pathophysiology with a focus on SCN1A mutations. J Child Neuro, 24(8S), 15S-23S. Available at: http://jcn.sagepub.com/content/24/8_suppl/15S.long [Accessed October 26, 2010]
[4]Vadlamudi L, et. al. (2010). Timing of de novo mutagenesis – A twin study of sodium-channel mutations. New Eng J of Med. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa0910752 [Accessed October 26, 2010]

Developments in Depression Research

by Vaibhav Mokashi

Findings by Yale University's Vanja Duric suggest that MPK-1, an enzyme of the MAPK signaling cascade, plays an important role in the deregulation of certain areas of the brain. Duric showed that MPK-1 expression increases during stressful situations and negatively regulates the MAPK pathway that is involved in neuronal plasticity, function and survival. Consequently, the negative regulation of MAPK decreases the growth and viability of neurons in the hippocampus – the region of the brain that plays a key role in depression. Further testing using rat models showed that chronic antidepressant treatments normalize stress-induced MPK-1 over expression. Dr. Duric's team believes that developing drugs that reduce MPK-1 expression in depressives will be much easier now that MAPK mechanisms are understood thoroughly.[1]

On a similar note, Dr. Alexander at Cornell successfully used gene therapy to reduce depression-like symptoms. In his animal model of depression, mice were missing the p11 gene, which regulates levels of serotonin, a neurotransmitter that is linked with mood, sleep and memory. Dr. Alexander's team used a viral vector to deliver a functioning copy of the gene into the defective mice to restore p11 expression and reduce depressive behaviour.[2] Overall, these exciting new developments in molecular neuroscience and pharmacogenomics have the potential to improve our understanding of depression and may lead to new treatment options.

[1]Alexander B, Warner-Schmidt J, Eriksson T, Tamminga C, Arango-Lievano M, Ghose S, Vernov M, Stavarache M, Musatov S, Flajolet M, Svenningsson P, Greengard P, & Kaplitt M. (2010). Reversal of Depressed Behaviors in Mice by p11 Gene Therapy in the Nucleus Accumbens. Science Translational Medicine, 2(54), 54-76. Available from: DOI: 10.1126/scitranslmed.3001079 [Accessed 1st November 2010].
[2]Duric V, Banasir M, Licznerski P, Schmidt HD, Stockmeier CA, Simen AA, Newton SS, & Duman RS. (2010). A negative regulator of MAP kinase causes depressive behavior. Nature Medicine. Available from: doi:10.1038/nm.2219 [Accessed 1st November 2010].

Poke-Free Glucose Monitoring for Diabetic Patients

by Shelly Chopra

Diabetics prick their fingers multiple times per day to monitor their blood glucose level. While this method may provide accurate measurements, the data obtained are of a discontinuous nature and prevent physicians from discerning glucose level trends. Over the past few years, continuous glucose monitoring (CGM) devices have been developed in response to this limitation of traditional glucometers. Unfortunately, a common requirement of CGMs is the use of external devices to record data, a criterion giving rise to potential infection.

In an attempt to overcome the shortfalls of current CGM and conventional monitoring devices, Shibata et al. designed a system that involves the implantation of biostable microbeads under the skin.[1] Shibata et al. first synthesized a fluorescent monomer that not only binds to glucose reversibly but also maintains its properties when immobilized on the surface of a polymer, such as a bead. The monomer was also designed with a high surface area, enabling easy access to glucose-binding sites. After integrating the fluorescent monomer into a microbead, the researchers tested its efficacy in mice by injecting the beads beneath the epidermis of each mouse's ear. As the fluorescent monomers proved highly responsive to glucose, Shibata et al. used fluorescent imaging to monitor continuous fluctuation in blood glucose levels. In regards to measurement accuracy, the glucose concentrations calculated by the fluorescence microscope were found to correlate closely with those obtained through blood tests.[1] Being comparably less invasive, coupled with a high degree of sensitivity, glucose monitoring via fluorescent microbeads may preserve the index fingers of 171 million diabetics from ever being poked again.[2]

[1]Shibata H, Heo YJ, Okitsu T, Matsunaga Y, Kawanishi T, & Takeuchi S. (2010). Injectable hydrogel microbeads for fluorescence-based in vivo continuous glucose monitoring. Proceedings of the National Academy of Sciences of the United States of America, 107(42), 17894. Available from: http://www.pnas.org/content/early/2010/09/27/1006911107.abstract. [Accessed 29 October 2010].
[2]Rathmann W, & Giani G. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care, 27(10), 2568-9.