TOXINS

OUABAIN: FROM POISON TO CONTRACEPTIVE

KEVIN CHEN

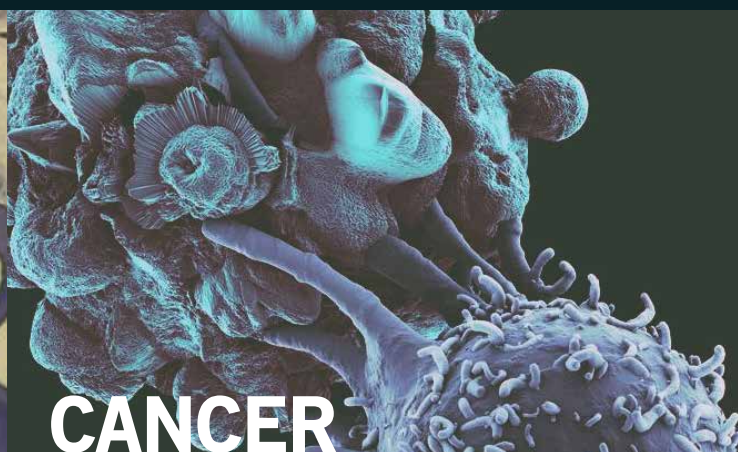
Despite the myriad of contraceptive methods designed for women, the options for men have generally relied on vasectomy or use of condoms.[1] Recently, however, researchers from the American Chemical Society have investigated the potential of introducing a third option based on analogues of ouabin, a plant-derived cardiovascular toxin traditionally used as a poison.[2,3]

Ouabain inhibits Na^+/K^+-ATPase, a protein expressed in almost all vertebrate cells in various isoforms to maintain resting membrane potential.[4,5] The purpose of this protein is to maintain resting membrane potential through sodium/potassium homeostasis. Of particular interest is the α4 isoform located only in mature sperm cells, where its activity maintains homeostatic conditions necessary for sperm survival.[5] Despite these attributes, ouabain remains a poor candidate for contraception due to serious clinical consequences of Na+/K+-ATPase inhibition, which may include hyperkalemia, cardiac arrhythmias, or death.[5]

In a study published in *The Journal of Medicinal Chemistry*, 32 heterogeneous ouabain analogues were created.[2] *In vitro* experiments with rat sperm revealed that the analogue with the highest affinity for the α4 isoform caused a reduction in the motility of sperm, hindering its ability to reach the egg.[2] The drug also decreased hyperactivation, compromising the sperm's ability to penetrate the zona pellucida, a thick membrane surrounding the egg.[2] Furthermore, *in vivo* experimentation revealed that oral administration to rats had no toxic effects and reduced both sperm count and motility.[2]

Despite these promising results, additional experiments are required, especially considering the potentially dangerous clinical consequences of oubain and its inhibition of Na^+/K^+-ATPase. Further research on the oubain analogue's safety, as well as its exact mechanism of action and its efficacy in human subjects will be needed to confirm or reject the possibility of a male contraceptive derived from this plant extract.

1. National Health Service. What is the male pill?. 11 Jul 2017. Available from: https://www.nhs.uk/conditions/contraception/male-pill/ [Accessed: 10th February 2018].
2. Syeda SS, Sánchez G, Hong KH, Hawkinson JE, Georg GI, Blanco G. Design, synthesis, in vitro and in vivo evaluation of ouabain analogs as potent and selective Na, K-ATPase α4 isoform inhibitors for male contraception. *Journal of Medicinal Chemistry.* 2018; 61(5):1800-1820.
3. Cassels BK. Analysis of a Maasai arrow poison. *Journal of Ethnopharmacology.* 1985;14(2-3):273-81. Available from: doi: 10.1016/0378-8741(85)90094-7.
4. Fürstenwerth H. Ouabain–the insulin of the heart. *International Journal of Clinical Practice.* 2010;64(12):1591-4.
5. Liu J, Shapiro JI. Regulation of sodium pump endocytosis by cardiotonic steroids: molecular mechanisms and physiological implications. *Pathophysiology.* 2007;14(3):171-81.



CANCER

A NEW PROMISE IN CANCER IMMUNOTHERAPY

JAMES YU

The immune system is naturally programmed to target and attack tumours using T lymphocytes. As tumours grow, however, they can inhibit immune cells and escape immune detection, creating an internal reservoir of inhibited T cells.[1] Immunotherapy, or the introduction of biological agents to boost immune function, has long been heralded as the holy grail of cancer treatment.[2] Unfortunately, many current approaches incur high costs, involve long wait-times, and present the possibility of overdriving the immune system.[3]

Using mice models, researchers at Stanford University developed a combination therapy of two immune-stimulating agents to be injected into solid tumours.[1] One agent, CpG, upregulates the expression of a receptor called OX40 on the surface of specific T cells. The other agent, an anti-OX40 antibody, stimulates the OX40 receptor and activates T cells within the tumour, allowing them to destroy cancerous cells.[4] These T cells can then leave the original tumour and attack other identical, cancerous cells in distant, untreated metastases. Remarkably, the therapy resulted in complete elimination of cancer in 87 of the 90 mice subjects and regression after a second injection in the three remaining mice.[1] This success can be balanced with safety, as the local administration of the treatment enables researchers to avoid overdriving the immune system and eliciting systemic side effects.

These results, despite their promise, must consider the significant differences between spontaneous tumours and transplanted tumours, which the initial experiments used.[3] Although the researchers eventually mimicked spontaneous tumourigenesis with mice lacking an oncogene, effects in these animal models may not necessarily translate to humans. Nonetheless, the impressive preliminary success achieved with this combination therapy and the well-characterized nature of its two agents have encouraged its clearance for a clinical trial of 15 patients with low-grade lymphoma.[1]

1. Staveley-O'Carroll K, Sotomayor E, Montgomery J, Borrello I, Hwang L, Fein S et al. Induction of antigen-specific T cell anergy: An early event in the course of tumor progression. *Proc Natl Acad Sci U S A.* 1998;95(3):1178–83.
2. Sagiv-Barfi I, Czerwinski DK, Levy S, Alam IS, Mayer AT, Gambhir SS et al. Eradication of spontaneous malignancy by local immunotherapy. *Sci Transl Med.* 2018;10(426):eaan4488.
3. Dempke WCM, Fenchel K, Uciechowski P, Dale SP. Second- and third-generation drugs for immuno-oncology treatment–The more the better? *Eur J Cancer.* 2017;74:55–72.
4. Voo KS, Bover L, Harline ML, Vien LT, Facchinetti V, Arima K et al. Antibodies targeting human OX40 expand effector T cells and block inducible and natural regulatory T cell function. *J Immunol.* 2013;191(7):3641–50.

ANTIBIOTICS

UNEARTHING NEW ANTIBIOTICS

JAMES YU

Internationally, more than 700,000 people die from antimicrobial-resistant bacterial diseases each year.[1] With superbugs developing resistance to even the antibiotic of last resort, vancomycin, scientists are racing to expand options. Currently, research is investigating the potential of antibiotics derived from natural products of bacteria residing within petri dishes. However, the diversity of bacteria being examined within cultures is limited, and rediscovery rates for antibiotics are high.[2]

Currently, researchers from Rockefeller University are extracting antibiotics from soil microorganisms.[3] Since only 1% of bacterial species in soil can be cultured in labs, the team has developed a method to extract and sequence DNA from soil without growing bacteria.[4] Specifically, the researchers inserted clusters corresponding to the production of antibiotics into bacteria; with this method, they discovered malacidin - a novel molecule similar to daptomycin. Experiments with Staphylococcus aureus (MRSA), a superbug resistant to many antibiotics, detected no resistance to malacidin. In fact, this antibiotic completely eliminated MSRA in rat subjects.[3]

Although malacidin is a promising solution for controlling gram-positive bacteria, it is ineffective against gram-negative bacteria, which are responsible for pneumonia and Lyme disease, for instance. New antibiotics for gram-negative bacteria needed, especially because their relatively impermeable cell wall grants allows them to be more antibiotic resistant.[3] Although it is impossible to conclude whether malacidin will be clinically useful, the methodology of this study may prove valuable to other scientists searching for antibiotics in unexplored environments, from deserts to oceans.

1. O 'neill J. Tackling drug-resistant infections globally: final report and recommendations the review on antimicrobial resistance. 2016; Available from: https://amr-review.org/sites/default/files/160518_Final paper_with cover.pdf [Assessed 2nd February 2018].
2. Reddy BVB, Kallifidas D, Kim JH, Charlop-Powers Z, Feng Z, Brady SF. Natural Product Biosynthetic Gene Diversity in Geographically Distinct Soil Microbiomes. *Appl Environ Microbiol.* 2012;78(10):3744–52.
3. Hover BM, Kim S-H, Katz M, Charlop-Powers Z, Owen JG, Ternei MA et al. Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens. *Nat Microbiol.* 2018;1.
4. Tringe SG, von Mering C, Kobayashi A, Salamov AA, Chen K, Chang HW et al. Comparative Metagenomics of Microbial Communities. *Science.* 2005;308(5721):554–7.

DIABETES

DIABETES – BLOOD, SWEAT, AND TEARS

KEVIN CHEN

Diabetes mellitus (DM), a metabolic disorder characterized by irregular insulin production or insulin resistance, affects over 350 million people worldwide.[1] Diabetic individuals must monitor their blood glucose levels several times a day, using a process that commonly involves pricking the skin and obtaining a small blood sample to test. Although effective, the frequency of self-monitoring has been reported to decrease over time, largely due to inconvenience.[2] Hence, there is a need for the development of a need to develop more pragmatic and continuous monitoring methods.

In recent years, the advent of wearable biosensor technology has allowed users to monitor their heart rates and physical activity levels more easily, even though current commercially available wearables are still unable to monitor the body's status on a molecular level.[3]

In a potentially revolutionary advancement, however, researchers have developed a new indium oxide nanoribbon field-effect transistor (FET) biosensor.[3] Used to amplify weak signals, a FET is a special type of transistor in which current flow is modulated by a transverse electric field and used to amplify weak signals.[4,5] Incorporating an on-chip gold side gate electrode, a natural chitosan film, and carbon nanotubes, this new device relies on the reactions between glucose in the fluid sample and glucose oxidase in the biosensor; the ensuing process produces an electrical signal that can be analyzed by the sensor for the detection of glucose concentrations from 10 nanomolar to 1 millimolar in the sweat, saliva, and tears of both diabetic and non-diabetic individuals. As researchers modify the design of the biosensor to fit the surface of an artificial eye and an artificial arm, this technology may be potentially worn as contact lenses or skin patches for the continuous monitoring of glucose levels.[3]

1. Lotfy M, Adeghate J, Kalasz H, Singh J, Adeghate E. Chronic complications of diabetes mellitus: A mini review. *Current Diabetes Reviews.* 2017;13(1):3-10.
2. Peel E, Douglas M, Lawton J. Self monitoring of blood glucose in type 2 diabetes: longitudinal qualitative study of patients' perspectives. *BMJ.* 2007;335(7618):493.
3. Liu Q, Liu Y, Wu F, Cao X, Li Z, Alharbi M et al. Highly sensitive and wearable In2O3 nanoribbon transistor biosensors with integrated on-chip gate for glucose monitoring in body fluids. *ACS nano.* 2018;12(2):1170-1178.
4. Shockley W. A unipolar" field-effect" transistor. *Proceedings of the IRE.* 1952;40(11):1365-76.
5. Rouse, M. Field-Effect Transistor (FET). 2005. Available from: http://whatis.techtarget.com/definition/field-effect-transistor-FET [Assessed 2nd February 2018].