

## Oxitec's genetically-modified mosquitoes: in the public interest?



December 2010

The UK biotech company Oxitec has recently released 3 million genetically-modified (GM) male mosquitoes as part of an open release field experiment in the Cayman Islands.

The GM mosquitoes produced by Oxitec mate with wild female mosquitoes but are genetically engineered so that most of their offspring die before adulthood. This is intended to reduce the population of the released mosquito species, which is a carrier of the dengue virus, and hence to reduce the incidence of this tropical disease. However, there are many unanswered questions about the impacts of this technology and concerns about the process for approving these experiments.

Further open releases of Oxitec's GM mosquitoes are planned for Malaysia in December 2010.

This briefing provides background information about the company, its technology, and its recent and proposed experimental releases of GM mosquitoes.

Key findings are:

- Oxitec is losing approximately £1.7 million a year and owes £2.25 million to a Boston multi-millionaire investor which it is due to repay by 2013;
- Oxitec's business model assumes its developing country customers will be locked in to ongoing payments for repeated releases of millions of GM mosquitoes, allowing it to repay this loan and pay dividends to its investors, including Oxford University;
- The company's first open field trials of 3 million GM mosquitoes have been undertaken in the Cayman Islands (a British Overseas Territory) - funded by UK charity the Wellcome Trust - without any consultation, public risk assessment, ethical oversight, or the consent of local people;
- Former UK science minister Lord Drayson and former President of the Royal Society Bob May have both acted as advisors to investors in the company (Oxford University Challenge Seed Fund and East Hill Management LLC respectively);
- The company has also received significant public subsidy, including more than £2.5 million in grants from the UK government-funded Biotechnology and Biological Sciences Research Council (BBSRC), mostly for joint projects with Oxford University;
- Oxitec has made misleading statements repeatedly in the media that its GM mosquitoes are sterile;

- Oxitec has played a key role in developing risk assessment processes for its own products and has omitted or downplayed some serious potential adverse effects of its technology in these risk assessment processes;
- Oxitec is developing a GM version of a second species of dengue-carrying mosquito (the Asian Tiger mosquito) because it is aware that this mosquito could occupy the ecological niche vacated by reductions in numbers of the first species it is targeting. This second species is more invasive and can carry more diseases;
- Decisions to invest in mass-production facilities for GM mosquitoes in Oxfordshire, speed Oxitec's products through regulatory processes, and begin experimental releases in open field trials have been taken by Oxitec's venture capital investors and grant funders in London, Oxford and Boston, rather than by the company's potential customers or people living in dengue-infected areas.

## About Oxitec

Oxitec is a spin-out company from Oxford University, based at Milton Park in Oxfordshire.<sup>1</sup> Isis Innovation (Oxford University's technology transfer arm) was responsible for helping to set up the company and assisting to obtain venture capital investment.<sup>2</sup> In August 2008, Oxford Spin-out Equity Management (OSEM) was set up to manage the University's shareholdings in its spin-out companies and seek ways of maximising the value of its equity stakes: Oxitec is now part of its portfolio.<sup>3</sup>

## Oxitec's technology

Oxitec's patented technique for genetically modifying insects is known as RIDL (*Release of Insects carrying a Dominant Lethal genetic system*). These GM insects are intended to be used as a form of biological control to reduce natural populations of the target insect when released into the wild.

Oxitec has developed a number of products incorporating its RIDL technology.<sup>4</sup> These include genetically-modified strains of the Yellow Fever mosquito (*Aedes aegypti*) and the Asian Tiger mosquito (*Aedes albopictus*): both of these species can transmit dengue fever. Oxitec also has novel strains of agricultural pest insects. A genetically-modified pink bollworm strain containing a heritable fluorescent marker and sterilised by exposure to radiation has been tested by the USDA in open field trials. However, pink bollworm containing the RIDL genetic trait has not yet been released in open trials. Genetically-modified Mediterranean fruit fly, Mexican fruit fly and olive fly have also been developed but have not yet been released.

The focus of this briefing is on Oxitec's lead strain of *Aedes aegypti*, OX513A, which has been released in open field trials in the Cayman Islands and is planned for release in field trials in Malaysia shortly.

The OX513A strain of the *Aedes aegypti* mosquito is genetically engineered to contain a red fluorescent marker and the RIDL 'conditional lethality' trait.<sup>5</sup> Conditional lethality means that the mosquitoes have been engineered to be able to survive to adulthood only in the presence of tetracycline (an antibiotic used to treat bacterial infections such as urinary tract infections, chlamydia and acne). GM mosquitoes are bred to adulthood

in the lab in the presence of the antibiotic and males are then released into the environment.

Before release, male and female mosquito pupae are separated mechanically. Sex separation by size sorting is expected to result in a population containing less than 1% females for release (less than 0.1% female if large males are also discarded).<sup>6</sup> The intention is to release only males because they do not bite and transmit disease. The released males mate with wild females and their progeny die as late larvae or pupae. Continual releases of sufficient numbers of RIDL males are expected to reduce the mosquito population and hence the transmission of disease.

The late lethality means that genetically-modified larvae will compete with wild mosquito larvae for resources, adding to the expected reduction in population compared to the alternative approach of releasing irradiated insects (irradiation of adult insects causes the progeny to die as embryos and not form larvae).<sup>7,8</sup> However, this means it is inaccurate to describe Oxitec's GM mosquitoes as sterile: they do reproduce but most of their progeny do not reach adulthood, usually dying at the late larvae/early pupae stage. Large numbers of dead GM mosquito larvae and pupae will result from a commercial-scale release programme and some genetically-modified pupae will also survive to adulthood (3 to 5% of the progeny of females which mate with GM males survive in Oxitec's laboratory experiments<sup>9</sup>).

Preliminary computer modelling by Oxitec suggests that a ratio of about six RIDL mosquitoes to one wild adult female should be maintained to eradicate a population of *Aedes aegypti* mosquitoes over a time period of just over a year: however, these figures and the best strategy for timing and maintaining releases are highly uncertain.<sup>10</sup> The female mosquito to human ratio in endemic areas is about ten to one and in this paper Oxitec suggests that 100 million to a billion GM mosquitoes should be stockpiled for a given project. Because mosquitoes reproduce continually, releases will need to be made frequently, probably weekly, to suppress the population.<sup>11</sup> In other more recent papers, the company suggests that eradication is unlikely and that continual releases will be needed to maintain suppression (but not eradication) of the mosquito population.<sup>12</sup>

The GM mosquitoes will be released into a complicated ecosystem, involving other mosquito species, predators and prey, the dengue virus, and the humans who are bitten. Because this system is poorly understood there remain unanswered questions about the impacts of the proposed releases, including:

- the numbers of GM mosquitoes that will be needed and the impacts of the large numbers of dead larvae and pupae and smaller number of surviving GM adults produced when they mate;
- whether other pests (especially the Asian Tiger mosquito *Aedes albopictus* which can transmit more diseases and is one of the world's most invasive species<sup>13</sup>) will move into the ecological niche left by the reduced population;
- whether the dengue virus will evolve in response to become more virulent<sup>14</sup>;
- whether there will be a reduction in herd immunity in the human population leading to an increase in disease transmission<sup>15</sup>.

Fluctuations in the mosquito population will effect these complex interactions as will any loss of effectiveness of the RIDL system over time, or difficulties scaling-up to large-scale production.

## Patents

The first patent relating to Oxitec's technology was filed in November 1999 by Isis Innovation, with Luke Alphey (Chief Scientific Officer at Oxitec) and Dean Thomas named as inventors (equivalent patents have been filed in a series of other countries including the US, Mexico and China).<sup>16</sup> Six subsequent patents relating to GM insect technology have been filed by Oxitec with Luke Alphey named as inventor.<sup>17</sup> Five further Oxitec patents relate to methods for detecting gene sequences which also have wider applications (the named inventor on these applications is Fu Guoliang).

## Oxitec's investors

Oxitec received £228,775 from the Oxford University Challenge Seed Fund (UCSF) in 2001 "at a critical time in its development".<sup>18,19</sup> The UCSF was set up following advice to the then New Labour government by biotech venture capitalist David Cooksey in 1988. Its role is to distribute investment from the UK Government, the Wellcome Trust and the Gatsby Charitable Foundation in order to help commercialise university research, with the aim of reinvigorating the UK economy.<sup>20</sup> Oxitec was incorporated as a Private Limited Company in August 2002.<sup>21</sup>

The company has raised venture capital in four funding rounds to date. In 2002 it received initial seed funding of £1.5 million from Oxford University and East Hill Management LLC of Boston. In June 2005 it secured a second round financing of £1.3 million from the original investors and Oxford Capital Partners<sup>22</sup> (which invested £550,000).<sup>23,24</sup> The company stated that the new funds would be used to progress its lead RIDL products (the Mediterranean Fruit Fly, the mosquito *Aedes aegypti*, and the Pink Bollworm) through regulatory programmes, and initiate research on new targets.<sup>25</sup> In October 2007 Oxitec received £1.5m in a private investment round led by Oxford Capital Partners who invested £1m, the remaining £0.5 million coming from Landon Clay of East Hill Management.<sup>26,27</sup> In December 2009 Oxitec closed a further investment round from both existing and new (unnamed) investors.<sup>28</sup> The company's accounts state that this fundraising round secured an additional £1.7 million of equity investment.<sup>29</sup>

In October 2010 Oxitec appointed Deloitte to assist in finding new equity capital to create increased production capacity for its GM mosquitoes for "a number of markets" in 2011.<sup>30</sup>

## Oxitec's grants

The UK government-funded Biotechnology and Biological Sciences Research Council (BBSRC) funded work undertaken by PhD students of Alphey's whilst he was still based at Oxford University covering: genes in fruit flies<sup>31,32</sup> and insect population control through transgenesis.<sup>33</sup> Oxitec has since secured a series of awards and grants from the BBSRC totalling more than £2.5 million (the majority in collaboration with Oxford University).

In June 2005, Oxitec was awarded US\$4.8m as part of an international consortium within the Grand Challenges for Global Health initiative, led by the Gates Foundation (in partnership with the Wellcome Trust, US Foundation for National Institutes of Health and Canadian Institutes for Health Research).<sup>34,35,36,37</sup> The Wellcome Trust's Director, Sir

Mark Walport, is also a member of the Grand Challenges for Global Health's Scientific Advisory Board.<sup>38</sup>

In February 2010, Oxitec was granted a Translation Award from the UK charity the Wellcome Trust to begin open field trials of the OX513A *Aedes aegypti* genetically modified mosquito (including trials in South East Asia in 2010).<sup>39,40</sup>

Oxitec's grants from the BBSRC are listed in full in the appendix. Other grants include:

- a three year World Health Organisation (WHO) grant from the Special Programme for Research and Training in Tropical Diseases (TDR) Innovative Vector Control Business Line, as part of an international consortium: the MosqGuide project (April 2008);<sup>41</sup>
- a South East England Development Agency (SEEDA) Research and Development grant to develop the RIDL technology for the control of the Asian tiger mosquito, *Aedes albopictus* (August 2009);<sup>42</sup>
- partnership in the Euros 8.5 million four year INFRAVEC (Research Capacity for the Implementation of Genetic Control of Mosquitoes) initiative under the EU's Framework 7 (FP7) research funding programme (September 2009).<sup>43,44</sup>
- a grant from the UK government-funded Technology Strategy Board (TSB)'s 'Feasibility Studies for Technology-Inspired Innovation' competition: to develop prototype equipment for use in mass-production of GM mosquitoes together with a manufacturing company (December 2009) (the TSB funds 75% of the project cost, up to around £25,000<sup>45,46</sup>)
- funding from the Technology Strategy Board (TSB) to develop RIDL technology in the tomato leaf miner, *Tuta absoluta*, jointly with crop protection company BCP Certis (July 2010).<sup>47,48,49</sup>

## Oxitec's debts and business model

Oxitec's 2009 accounts state that the additional capital it raised in December 2009, together with a convertible loan facility of up to £846,000 secured in February 2010 was considered to be sufficient to fund the company's operations until at least the end of the first quarter of 2010.<sup>50</sup> Footnote 12 to the accounts states: "*During the course of the prior year, the company was provided with a £1,500,000 unsecured loan facility by East Hill Venture Fund LP, a business which is controlled by LT Clay, a director of Oxitec Limited. This loan is repayable in 2013. At 31 December 2009, £1,500,000 (2008 £1,000,000) of this facility had been drawn down by the company. During the year the company was provided with and drew down a further £750,000 loan secured by way of debenture over the company's assets. During the year interest charges of £131,800 (2008 £18,405) were accrued and added to the amount of the outstanding loans*".

Oxitec made a loss in 2008 and 2009 of £1.7m a year: no dividends were paid to its investors.<sup>51</sup> The company does not appear to have raised new capital since December 2009 and is presumably surviving based on the Wellcome Trust grant it secured to conduct the open field trials, as well as its other grants from the UK government-funded BBSRC and TSB, the Gates Foundation, EU and WHO/TDR.

David Bott of the UK Technology Strategy Board (TSB) reports a debate at Oxford Spin-out Equity Management (OSEM)'s conference on 22<sup>nd</sup> September 2009; "*Oxitec, has a*

*challenging business model. ...There was quite a debate about who the customer was and how to monetise the product - or is it a service?"<sup>52</sup>*

It is clear that Oxitec expects to gain income from continual releases of GM mosquitoes in large numbers in several partner countries and that it is attempting to speed its products through the regulatory process in order to repay its loan and start generating income for its venture capital investors. In order for its business model to be viable it will need to lock its customers – presumably developing country governments – into a system of repeated ongoing payments. Even if there are no adverse effects, releases of GM mosquitoes will need to be continual to avoid resurgence in the mosquito population.

Oxitec is now pioneering mass-rearing at its facility in Oxfordshire. This facility will serve as the primary production site and eggs produced in the UK will be shipped under permit to countries worldwide. The company states that local facilities will be established to increase numbers to meet the demands of the local release programmes.<sup>53</sup>

The decisions to invest in these production facilities, speed Oxitec's products through regulatory processes, and begin experimental releases in open field trials have been taken by Oxitec's venture capital investors and grant funders in London, Oxford and Boston, rather than by the potential customers or people living in dengue-infected areas.

### **Friends in high places**

The then UK science minister Lord Paul Drayson visited Isis Innovation on January 23<sup>rd</sup> 2009. During his visit he received an update from Oxitec.<sup>54</sup> The company received its first payments from the Oxford University Challenge Seed Fund (UCSF) in 2001, when Drayson was a member of the UCSF board. Drayson's own biotech investments have been repeatedly criticised by the British press since it exposed that his own Oxford University spin-out company Powderject won a lucrative government contract shortly after he made a donation to the Labour Party (which was then in power).<sup>55,56,57</sup> One article has suggested that he saved £1 million in tax by setting up a charity to manage his biotech investments.<sup>58</sup>

Oxford Capital Partners offers investors a variety of tax benefits including 20% income tax relief (on investments up to £500,000); tax-free profits and exemption from inheritance tax (after two years).<sup>59</sup> Names of its investors are not publicly available.

The Managing Member, co-founder, and Chairman of East Hill Management Company LLC is Boston multi-millionaire Landon T Clay.<sup>60,61,62</sup> Clay is a member of the Oxitec Board.<sup>63</sup> Bob May (now Lord May of Oxford) is listed by Business Week as a member of East Hill Management LLC's scientific advisory board<sup>64</sup> but it also states he is President of the Royal Society (Britain's top scientific society), a position which he held from 2000-2005, so it is unclear when he joined the Board and whether he has now left. No current link with East Hill Management is declared in May's entry in the Lords' Register of Interests.<sup>65</sup> May is a former Government Chief Scientist and a current member of the House of Lords. He is Professor Emeritus at the University of Oxford Zoology Department<sup>66</sup>, where Oxitec's founder Luke Alphey is a Visiting Professor.<sup>67</sup> Alphey was involved in preparing a 2001 Royal Society report on GM animals, which included a section on GM insects.<sup>68</sup> Co-author Peter Goodfellow (then employed by GlaxoSmithKline) is also a Fellow of the Royal Society (FRS). He is married to Julia

Goodfellow who was Chief Executive of the BBSRC from 2002 to 2007 and is also a member of the SEEDA Advisory Board (both bodies have given grants to Oxitec).<sup>69</sup>

In November 2007 the World Economic Forum selected Oxitec as one of its Technology Pioneers: Alphey attended the Davos meeting in 2008 and 2009.<sup>70,71</sup>

Oxitec is a customer of Ansteadbrook management consultancy, established in 2004 by Colin Ruscoe, former site manager at Syngenta Crop Protection.<sup>72</sup> Ruscoe is Chairman of the British Crop Production Council. Ansteadbrook's other customers include Syntech Research (where Ruscoe is Director for Europe and Africa) and Syngenta Seeds. Syntech Research provides product development and regulatory services to the agricultural, biotechnology and food industries as well as government bodies and agricultural commodity suppliers.<sup>73</sup> In 2005 Ruscoe joined the Executive and Scientific Committees of the Innovative Vector Control Consortium (IVCC) to develop commercial partnerships and apply grants (including \$50m from Bill and Melinda Gates Foundation) to discover and deliver new chemical products and information systems for elimination of insect vectors of malaria and dengue. Oxitec obtained its consortium funding from the Grand Challenges in Global Health, led by the Gates Foundation, in 2005. The IVCC is also funding Syngenta to develop new insecticides for malaria mosquito control.<sup>74</sup>

Oxitec's Chief Executive Officer, Hadyn Parry, and Regulatory Affairs Manager Camilla Beech are both former employees of Syngenta.<sup>75</sup> Oxitec's Chief Executive Officer in Malaysia, Dr. Seshadri S. Vasan, is a former employee of the management consultancy firm McKinsey.<sup>76</sup> Oxitec's business development manager for the Americas from December 2007 to February 2009, Joachim Prudencio Leao, lists his clients during this time on his CV as Fiocruz, Health Ministry, USP, Syngenta, Embrapa and Moscamed do Brasil, and one of his roles as facilitating the adoption of Oxitec's vector control technology in Brazil.<sup>77</sup>

## **Role in risk assessment**

The Biotechnology and Biological Sciences Research Council (BBSRC) reports that Oxitec's founder Luke Alphey: *"is also working towards developing regulatory frameworks for GM insects internationally and within a number of countries including the USA"*.<sup>78</sup>

Alphey's webpage at the University of Oxford states that he is a member of the World Health Organisation (WHO) Scientific Working Group on Dengue (since 2006) and a member of the NAPPO Expert Working Group on RSPM 27 ("Importation and Confined Release of Transgenic Arthropods in NAPPO Member Countries") (since 2006).<sup>79</sup> (NAPPO is the North American Plant Protection Organisation: member countries are Canada, the US and Mexico). He contributed to the WHO's 2010 report on GM mosquitoes.<sup>80</sup>

Oxitec's Regulatory Manager, Camilla Beech represented the company in an open-ended online forum on specific aspects on risk assessment (including GM mosquitoes), convened under the Cartagena Protocol on Biosafety, an international treaty under the UN Convention on Biological Diversity.<sup>81</sup> The open-ended online forum provided input into the work of the Ad Hoc Technical Expert Group on Risk Assessment and Risk Management under the Cartagena Protocol on Biosafety, which has produced risk assessment guidance for GM mosquitoes.<sup>82</sup>

Beginning in 2007, Oxitec and the WHO Collaborating Centre for Vectors based at the Institute for Medical Research (IMR) in Malaysia conducted three intensive workshops on risk assessment of GM mosquitoes attended by delegates from Oxitec and the IMR and experts from the UK, Malaysia and India and later Thailand, USA, Zambia and Zimbabwe (in 2007, and July and November 2008).<sup>83,84,85,86</sup> According to Oxitec, the third workshop “*helped build the capacity of scientists and regulators in risk assessment and management to facilitate decision making process under the Biosafety Act*”. Seventy participants from local universities, research institutes and government agencies who are conducting research and development on genetically modified organisms actively participated in the workshop. Among the invited faculty members were Oxitec’s Seshadri Vasani and Camilla Beech (who is described incorrectly as “*a regulator from the United Kingdom*” in the Malaysian Government’s Biosafety Newsletter<sup>87</sup>). The workshop was carried out under the NRE-UNDP-GEF (Malaysian Ministry of Natural Resources and Environment, UN Development Programme and Global Environment Facility) biosafety project ‘Support to Capacity Building Activities on Implementing the Cartagena Protocol on Biosafety and the Malaysian Biosafety Act’. The new Malaysian Biosafety Act was passed in 2007 and implemented in December 2009. A further NRE-UNDP-GEF workshop on Risk Communication on Transgenic Insects was held in Malaysia in March 2010, led by Oxitec’s Seshadri Vasani.<sup>88,89,90</sup> A report of this meeting does not appear to be publicly available.

In September 2008, Oxitec co-organised a symposium with academic institutions in India on dengue and other neglected diseases.<sup>91</sup> In 2008/09 further symposia were held in Brazil, India and Malaysia.<sup>92</sup>

Oxitec is a member of the MosqGuide project, funded since 2008 by the WHO/TDR (a Special Programme for Research and Training in Tropical Disease). It aims to develop guidance for disease-endemic countries to consider the risks and benefits of the use of innovative genetic control methods for mosquito vectors of human diseases – specifically malaria and dengue.<sup>93,94</sup> The project involves partners at Imperial College (London, UK), the Instituto Nacional de Salud Publica (Mexico), the Gorgas Institut (Panama), Mahidol University (Thailand), University de Sao Paulo (Brazil), the University of Nairobi (Kenya) and an Emeritus Professor in India (Dr Rachel Reuben). The MosqGuide project is running biosafety courses in Africa, Asia and Latin America.

### **Open field trials in the Cayman Islands**

Oxitec conducted its first open field trials of any RIDL insect in the Cayman Islands, a British Overseas Territory. A small trial of Oxitec’s RIDL strain OX513A of *Aedes aegypti* mosquito was conducted in late 2009 and a larger release from May to October 2010, following funding from the Wellcome Trust and in collaboration with the Mosquito Research and Control Unit of Grand Cayman (MRCU).<sup>95</sup> These are the first releases of GM mosquitoes anywhere in the world and have been conducted without proper public debate, ethical oversight or parliamentary or scientific scrutiny.

On 2<sup>nd</sup> October 2009, the Director of MRCU Dr. Bill Petrie told the Cay Compass that any decision to go ahead with releasing GM mosquitoes would be subject to budget concerns, logistics and priorities; a permit would also have to be obtained from the Department of Agriculture and he did not know how much the undertaking would cost at



this point in time. However, a small-scale trial then took place in late 2009 and the further releases in 2010, without any public consultation.

A total of three million mosquitoes were released from May to October on a 16-hectare site, in batches three times a week.<sup>96,97</sup> Oxitec claims (based on unpublished preliminary results) that the number of mosquitoes in the area was reduced by 80% compared to a neighbouring untreated site. On 12 November 2010, the Wellcome Trust helped the company to generate positive publicity for the Cayman Island trials and its proposed Malaysian trials, at a press conference in London.<sup>98,99</sup> However, lack of public consultation for the Cayman Islands experiments has been strongly criticised by the leader of the Gates Foundation funded project in which Oxitec is a partner.<sup>100</sup>

The Cayman Islands does not have any biosafety laws and is not covered by either the international Cartagena Protocol on Biosafety or the Aarhus Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters, to which the UK is a party.<sup>101</sup> These conventions would have required publication of and consultation on an environmental risk assessment prior to release. Instead, the only regulatory requirements were a local permit from the Cayman Islands Agriculture Department and a notification of transboundary movement of a GMO (the GM mosquito eggs sent by Oxitec to Grand Cayman) under Regulation (EC) 1946/2003.<sup>102</sup> Neither of these documents appears to have been published. The UK Government has stated that this is a matter for the Cayman Islands and that the Foreign and Commonwealth Office (FCO) had no discussions in advance of the shipment of the GM mosquito eggs or their release.<sup>103</sup>

Informed consent does not appear to have been obtained from local people although consent to medical research is a requirement of the World Medical Association's Helsinki Declaration (which covers the ethical responsibilities of medical professionals).<sup>104</sup> Dengue is not endemic to the Cayman Islands but three cases occurred in January 2010 (confirmed by lab tests in March<sup>105</sup>) and it is unclear to what extent the trials relied on the assumption that Grand Cayman was then dengue-free.<sup>106</sup>

Misleading reporting by the journal Nature on its website referred to the release of the mosquitoes as having "*successfully wiped out dengue fever in a town of around 3000 people*" as well as to the insects being sterile.<sup>107</sup> Luke Alphey also described the mosquitoes as sterile in radio and television interviews.<sup>108,109</sup>

The only public information that appears to have been provided was a video entitled "MRCU sterile mosquitoes", which does not mention that the mosquitoes are genetically-modified and also repeatedly refers to them as sterile.<sup>110</sup> The video was put on the Cayman Islands Government Information Service (GIS) website on 4<sup>th</sup> October 2010, after the releases had already taken place.<sup>111</sup> Oxitec's press release in November 2010 is also misleading, claiming that the GM mosquitoes are "*genetically sterile*" and that females mating with sterile males "*will have no offspring*".<sup>112</sup>

The releases were not discussed or debated in the Cayman Islands' parliament.

Dr Petrie of the MRCU has continued to defend the trials despite criticism in the Cayman Islands press.<sup>113,114,115</sup>

## Planned field trials in Malaysia

Field trials of Oxitec's lead strain of *Aedes aegypti*, OX513A were approved in Malaysia in early October 2010 by the National Biosafety Board, and are planned for December 2010. The Institute for Medical Research (IMR), part of the Ministry of Health, made the application for approval of the field trials.

Unlike the Cayman Islands government, the Malaysian government is a party to the Cartagena Protocol on Biosafety and has enacted its national law on biosafety in the form of the Biosafety Act 2007. It conducted a public consultation about the proposed trials in the summer of 2010, inviting comments and views from the public over a one-month period.<sup>116</sup> It has also held a question and answer session for members of the press and placed conditions on the experimental releases.<sup>117</sup> For example, the decision states that: "*It is mandatory that the applicant through a public forum obtains prior consensus and approval from the inhabitants in the release sites*"; and requires the release site to be free of dengue for at least 3 months before the trial.<sup>118</sup> However, there remain concerns that the public consultation process was inadequate and that the risk assessment process has not been sufficiently precautionary.<sup>119</sup>

Oxitec has clearly played a major role in contributing to the risk assessment process for the Malaysian trials. The report of the NRE-UNDP-GEF workshop it helped run on Risk Assessment of Transgenic Insects in Malaysia in November 2008 omits some serious potential risks and downplays others.<sup>120</sup> For example, the workshop report:

- Describes the risk of an increase in the population of Asian Tiger mosquitoes (*Aedes albopictus*) as 'medium' but states that developing a genetically-modified *Aedes albopictus* strain should be considered as the response to this;
- Considers dead larvae only as a positive benefit to feeding fish;
- Omits the question of whether mosquito suppression will result in loss of human population immunity, although this is cited as a potential issue in other Oxitec-authored papers<sup>121</sup> and described elsewhere as "*among the most important unanswered questions in dengue epidemiology and GMM [Genetically Modified Mosquito]-based control approaches*"<sup>122</sup>;
- Fails to consider the possibility that the dengue virus may evolve to become more virulent (which is considered a lower risk with population suppression approaches, such as Oxitec's, than with other GM approaches, but which is still at an early stage of study<sup>123</sup>).

It is of particular concern that Oxitec describes the Asian Tiger mosquito *Aedes albopictus* (which is native to Malaysia) as a "*less anthropophilic, less effective vector*"<sup>124</sup> (i.e. less people loving and less effective at transmitting disease) when, elsewhere, Oxitec notes that mutation of the chikungunya virus appears to have considerably enhanced its infectivity in *Aedes albopictus*, leading to several outbreaks and one epidemic of this disease.<sup>125</sup> A European report describes *Aedes albopictus* as an aggressive biter that poses a severe nuisance to humans, can transmit at least 22 diseases and is one of the 100 world's most invasive species.<sup>126</sup> Oxitec's genetically-modified *Aedes albopictus* strain OX3688 is currently under development.<sup>127</sup>

## Conclusions

The first releases of GM mosquitoes anywhere in the world have taken place without any independent scrutiny or public consultation in the Cayman Islands. The secrecy and timetable have been driven by the financial needs of Oxitec and its venture capital investors, rather than by input from its potential customers or people affected by the dengue virus. Although Oxford University and the Wellcome Trust have funded Oxitec and its experimental trials, neither body appears to have imposed any ethical requirements on the company.

Although the government of Malaysia has taken a much more responsible approach, discussions around the risk assessment process appear to have been unduly influenced by Oxitec, through its role in leading and reporting the findings of the NRE-UNDP-GEF risk assessment workshop held in Malaysia. It is also unclear what role Oxitec has played in supporting the IMR's application for approval of the field trials. The informed consent of local people will depend on whether they are given transparent and comprehensive information about the proposed experiments, in line with the requirements of the Declaration of Helsinki. Whether the process of obtaining the consensus and approval of the local inhabitants is conducted to the highest standards remains to be seen.

Oxitec's business model involves locking its customers into regular payments for weekly GM mosquito releases in order to continue to suppress the population of wild mosquitoes. Its species-specific approach carries the danger that other more invasive and potentially more dangerous disease-carrying mosquito species will move into the ecological niche vacated by the reduced population. Oxitec sees this as a further business opportunity, allowing the development and sale of another GM mosquito product: but the costs, risks and potential failure of such a product to tackle this expected future problem have yet to be properly considered.

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## Appendix: Oxitec's BBSRC grants

The following grants have been made to Oxitec and partners by the UK government-funded Biotechnology and Biosciences Research Council (BBSRC):

- a 3½ year grant of £163,064 (to Luke Alphey of Oxitec via the University of Oxford) to research genes in fruit flies (October 1999);<sup>128</sup>
- a three year grant of £316,124 (via the University of Oxford) to research *A genetic approach to containment and pest control* (March 2002);<sup>129</sup>
- a two year research grant of £231,674 under the Small Business Research Initiative (SBRI) to develop *Improved transposon stability* (June 2004);<sup>130</sup>
- a three year PhD studentship, supervised by Alphey at the University of Oxford: *Mathematical modelling of novel pest control strategies*<sup>131</sup> (October 2004);
- a 3½ year £231,530 grant to research a protein in fruit flies, via the University of Oxford jointly with DH Bennett at the University of Liverpool (July 2004);<sup>132</sup>
- a three year PhD studentship, supervised by Alphey at the University of Oxford: *Development of a RIDL-based genetic sexing mechanism in Ceratitis capitata* (the Mediterranean fruit fly) (October 2004);<sup>133</sup>
- a three year PhD studentship, supervised by Alphey at the University of Oxford: *Identification and characterisation of the major insecticide detoxification genes in insects* (October 2004);<sup>134</sup>
- a three year research grant (via the University of Oxford) of £320,552 for *Genetic control of agricultural pest insects* (March 2005);<sup>135</sup>
- a two year grant of £230,795 under the BBSRC's Small Business Research Initiative for *Improved insect transformation* (April 2005);<sup>136</sup>
- a three year PhD studentship, supervised by Alphey at the University of Oxford: *Modelling optimal strategies for novel genetics-based pest management strategies* (October 2005);<sup>137</sup>
- a three year PhD studentship, supervised by Alphey at the University of Oxford: *Genetic control of the Codling moth (Cydia pomonella)* (October 2005);<sup>138</sup>
- a BBSRC Industrial Case Studentship (2006);<sup>139</sup>
- a £5,000 (runner-up) Innovator of the Year award to Luke Alphey (March 2009);<sup>140, 141, 142, 143</sup>
- two four year £70,820 BBSRC Industrial Case studentships with SP Sinkins at Oxford University on *Improved transposon stability in insect transgenesis* and *Genetic control of the diamondback moth Plutella xylostella* (October 2007).<sup>144, 145, 146</sup>
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- three four year £74,410 BBSRC Industrial Case studentships with SP Sinkins at the University of Oxford on *Mass-rearing high-quality insects for field applications; Applied insect genetics and functional conservation of regulatory*

*elements between taxa; and Fitness assessment of insect genetic replacement systems* (October 2009);<sup>150,151,152</sup>

- a three year £322,120 BBSRC cross-disciplinary collaborative LINK project with RB Bonsall of the University of Oxford on *Integrating ecology and genetics for insect pest control* (June 2010);<sup>153</sup>

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