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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Global Health Technologies Coalition present report to US government

A new report has been released that reviews US governmental research funding and suggests areas for improvement.

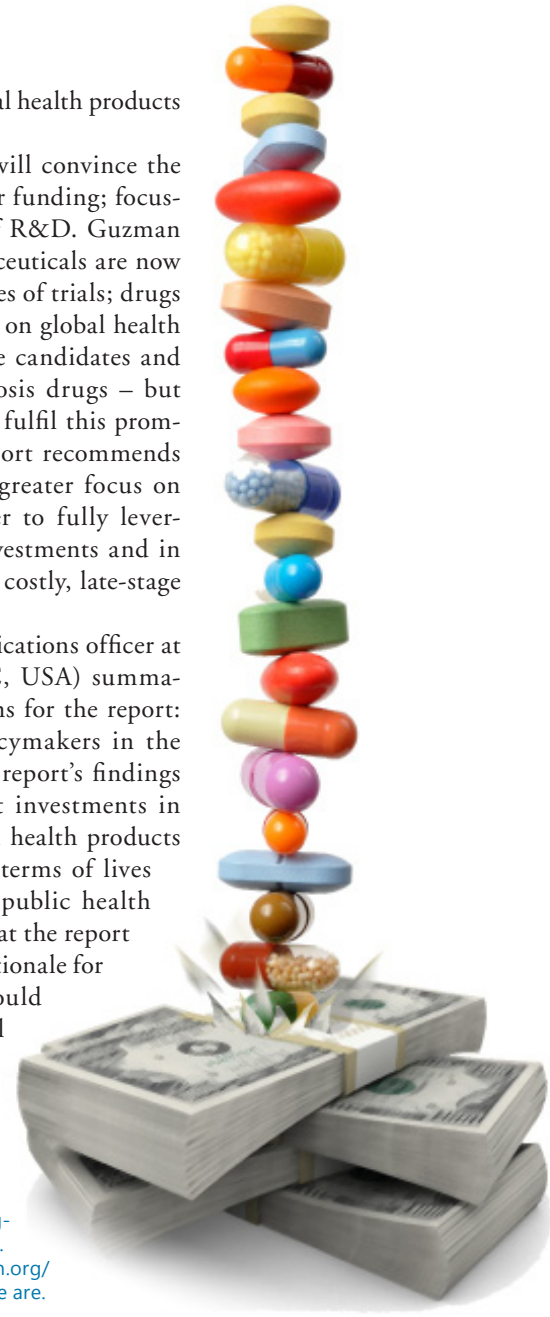
The Global Health Technologies Coalition (GHTC) and Policy Cures have recently released a report reviewing the US government's spending on global health R&D over the last 10 years. Their report shows the great impact this funding has; but urges the US government to focus their efforts more on clinical trials, to enable the translation of basic research into new pharmaceuticals.

The GHTC is a group of 40 non-profit organizations, including the Bill & Melinda Gates Foundation who also fund the coalition. Policy Cures is an independent health promotion charity, with offices based in Sydney (Australia) and London (UK). Both organizations aim to increase awareness of the need for global health research, in order to create pharmaceuticals to save lives in the developing world.

The report shows that the US government is funding inconsistently across the R&D process – with two-thirds of total funding aimed at basic research compared with only one-fifth going towards funding clinical studies in humans. In addition, looking at the total amount of funding that groups receive from the US government, 66% of funding received by basic reseasech is from the government, compared with only 39% in clinical research. Speaking exclusively to *Clinical Investigation,* Javier Guzman, director of research at Policy Cures (London, UK), explained: "It [the US government] is relying on others – like the Bill & Melinda Gates Foundation and industry – to translate new knowledge and leads into new technologies for patients. This is notable and unlikely to be sustainable given that clinical development is not only the most expensive stage, but is currently also the most in need of funding as more global health products enter expensive final trials."

It is hoped that the report will convince the US government to modify their funding; focusing more on the later stages of R&D. Guzman explained that various pharmaceuticals are now entering the expensive late stages of trials; drugs that would have a great impact on global health – including three HIV vaccine candidates and a new generation of tuberculosis drugs – but require appropriate funding to fulfil this promise. As he explained: "The report recommends that US government needs a greater focus on translational research in order to fully leverage its global health R&D investments and in particular increase funding for costly, late-stage clinical trials."

Kimberley Lufkin, communications officer at the GHTC (Washington, DC, USA) summarizes the coalition's expectations for the report: "The GHTC hopes that policymakers in the US Government will take the report's findings as compelling proof that past investments in research to develop new global health products are incredibly worthwhile, in terms of lives saved, disease prevented and public health cost savings. We also believe that the report provides decisive and crucial rationale for why the US Government should sustain its support for global health R&D – and increase this funding where possible."



– Written by Alice O'Hare

Sources: Global Health Technologies Coalition press release. www.ghtcoalition.org/press-release-saving-lives-and-creating-impact.php. GHTC. About the coalition. www.ghtcoalition.org/about-ghtc.php. Policy Cures. Who we are. www.policycures.org/whoweare.html

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Afinitor approved by the US FDA for the treatment of non-cancerous kidney tumors

The pharmaceutical Afinitor™ (everolius) has recently been approved by the US FDA for treatment of non-cancerous kidney tumors. The drug, an oral inhibitor of mTOR kinase, is marketed by Novartis (East Hanover, NJ, USA).

The rare genetic disease tuberous sclerosis complex (TSC), which affects approximately 40,000 people in the USA, causes growth of non-cancerous tumors in the kidney, brain and other vital organs. These tumors, although not malignant, cause significant damage to the organ(s) in which they are located, jeopardizing their functions. A total of 70–80% of patients with TSC develop kidney problems in this manner. Afinitor works to prevent formation of these tumors, by blocking the uncontrolled activity of mTOR kinase, which is involved in their development.

The drug was given orphan drug status by the FDA, a designation given to pharmaceuticals that could treat a disease affecting fewer than 200,000 patients across the USA. The application was reviewed with priority and completed within 4 months. As Richard Pazdur, director of the Office of Hematology and Oncology Products at the FDA Center for Drug Evaluation and Research, explained: "This approval underscores the FDA's commitment to the development of drugs for rare diseases with significant unmet medical needs."

> "Afinitor works to prevent formation of these tumors, by blocking the uncontrolled activity of mTOR kinase, which is involved in their development"

Afinitor was shown to be safe and effective in a double-blind, placebo-controlled clinical trial of TSC patients. These patients suffered from kidney tumors that did not require immediate surgery. Out of the 118 patients included in the study, two-thirds were given the pharmaceutical and one-third a placebo. Early results showed a high rate of tumor reduction in the patients taking the drug, again driving Afinitor's accelerated approval by the FDA; however Novartis is required to monitor the trial patients for at least 4 years to fully determine the length of these responses and the overall progression of these patients.

– Written by Alice O'Hare

Source: FDA press release. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302048.htm

Levofloxacin gains US FDA approval to treat plague

The US FDA has approved levofloxacin (Levaquin®; Janssen Pharamaceuticals, Inc.) to treat the causative agent of plague, the bacterium *Yersinia pestis*. Levofloxacin has also been approved to lower the rate of contracting plague after exposure to the bacteria.

Levofloxacin is a synthetic chemotherapeutic antibiotic belonging to the fluroquinolone class of drugs. Initially approved in 1996, the antibiotic is now used to treat a wide spectrum of bacterial infections, particularly when infection is severe and the patient has failed to respond to other antibiotic classes. Levofloxacin is associated with a variety of severe side effects and carries several FDA black box warnings. With this new approval, levofloxacin will join three other approved antibiotics for the treatment of plague; streptomycin, doxycycline and tetracycline.

Infection with *Y. pestis* causes three forms of plague; septicemic, pneumonic and bubonic. Plague, although notorious throughout history, is now a rare disease. However, the disease remains a concern as many animal species still carry the infection, which is also still endemic in some countries. The WHO estimates human infection to be approximately 1000–2000 cases per annum. Another concern stems from the use of *Y. pestis* in biological weaponry; in fact the CDC classifies *Y. pestis* as a category A pathogen.

> "...all animals treated with levofloxacin for 10 days survived."

For ethical reasons, the FDA approval for levofloxacin was based on evidence of efficacy collected in 24 African Green Monkeys. The monkeys received a head-only aerosol challenge with 3–125 LD50 doses of the *Y. pestis* strain CO92. Animals with a substantial increase in body temperature received intravenous dextrose controls or levofloxacin. All control animals died of severe pneumoic plague within 5 days of aerosol exposure, whereas all animals treated with levofloxacin for 10 days survived.

Fred Koster, Principle Investigator on the study, based at Lovelace Respiratory Research Institute (NM, USA), discussed the study's findings with *Expert Review of Anti-infective Therapy* – "Primary pneumonic plague is rare … but the potential for its appearance in bioterror attacks required a search for an antibiotic that was capable of curing clinically advanced infection and available in all hospitals. Levofloxacin is widely available, has an extensive safety record and achieves good tissue levels in the lung. Therapy with intravenous levofloxacin began after the onset of fever, when pneumonia was established and death was inevitable within 60 h, levofloxacin cured every infection."

– Written by Caroline Purslow

Sources: Layton RC, Mega W, McDonald JD *et al.* Levofloxacin cures experimental pneumonic plague in African Green Monkeys. *PLoS Negl. Trop. Dis.* 5(2), e959 (2011).

New study provides reassurance that the shingles vaccine is safe

A recent study examining data from 193,083 adults aged 50 years and older who were vaccinated with the herpes zoster vaccine between January 2007 and December 2008, has found the vaccine to be generally safe and well tolerated.

The herpes zoster vaccine was licensed in 2006, but despite the Advisory Committee on Immunization Practices recommending the vaccine for healthy people aged 60 years and older, the uptake has not been fast. In 2011, the US FDA approved the vaccine for use in individuals 50–59 years of age. The study results provide important safety data for people in this age group, as well as adults aged 60 years and over.

> "The study results provide important safety data for people in this age group, as well as adults aged 60 years and over."

A small, increased risk of allergic reactions 1–7 days after vaccination was identified. This reaction was generally a minor local reaction at the injection site in the form of redness and pain. There were no major serious adverse events and all of the local reactions were treated in outpatient settings and did not require hospitalization.

The data analyzed in this study were collected from eight institutions participating in the Vaccine Safety Datalink project. The Vaccine Safety Datalink project is a collaborative effort between the CDC and integrated care organizations. The project identifies and analyzes gaps in scientific knowledge about any rare and serious events that occur following immunization.

> "A small, increased risk of allergic reactions 1–7 days after vaccination was identified."

Shingles is an illness that commonly affects older people. The condition is, like chicken pox, caused by the herpes zoster virus and results in a painful and contagious rash and may even cause nerve damage.

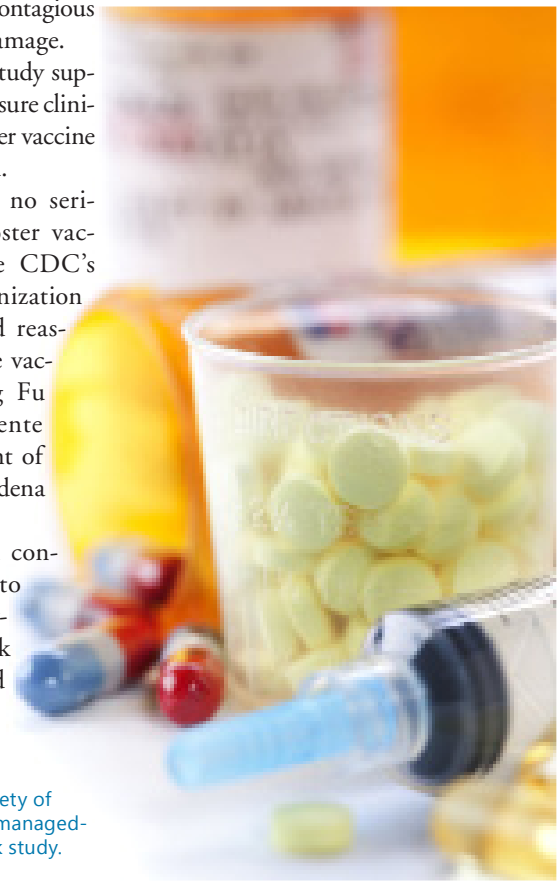
The promising results of this study support the findings from the prelicensure clinical trials, concluding that the zoster vaccine is generally safe and well-tolerated.

"It's good to know there is no serious adverse reaction to the zoster vaccine. The study supports the CDC's Advisory Committee on Immunization Practices' recommendation and reassures the general public that the vaccine is safe," explained Hung Fu Tseng, from Kaiser Permanente Southern California Department of Research and Evaluation in Pasadena (CA, USA).

"The elderly population can consider talking to their doctor to evaluate the possibility of receiving the vaccine to reduce the risk of the debilitating condition," said Tseng.

– Written by Laura McGuiness

Source: Tseng HF, Liu A, Sy L *et al.* Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study. *J. Inter. Med.* 271(5), 510–520 (2012).



Votrient approved by the US FDA

The US FDA has recently approved Votrient™ (pazopanib) for the treatment of advanced soft tissue sarcoma, in patients who have previously received chemotherapy. The pharmaceutical, administered as an oral pill and marketed by GlaxoSmithKline (NC, USA), hinders tumor growth by interfering with angiogenesis – the process of blood vessel growth.

Votrient was assigned orphan drug status for the application, a designation given to a drug that aims to treat a disease affecting fewer than 200,000 patients across the USA. In the USA, soft tissue sarcoma affects approximately 10,000 people every year. The disease consists of various subtypes, and in this instance, Votrient has been approved for more than 20 of these; however its efficacy was not tested for adipocytic soft tissue sarcoma or gastrointestinal stromal tumors.

The efficacy and safety of Votrient was proven in a single placebo-controlled clinical trial with 369 patients. The study measured progression-free survival and showed that the disease did not progress for a median of 4.6 months, compared with 1.6 months, for patients taking Votrient and placebo, respectively.

The director of the Office of Hematology and Oncology Products at the FDA's Centre for Drug Evaluation and Research, Richard Pazdur, explained the significance of this approval "Soft tissue sarcomas are a diverse group of tumors and the approval of Votrient for this general class of tumors is the first in decades."

– Written by Alice O'Hare

Source: FDA press release: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302065.htm

American Heart Association presents new data on anticlotting agents

New research suggests an increased risk of stroke after anticlotting drug administration is stopped.

In a recent American Heart Association 'Emerging Science' Series webinar, a group of researchers presented their work investigating the risk of stroke after patients stop taking anticlotting pharmaceuticals. Two such agents were investigated – rivaroxaban and warfarin – and the researchers' findings suggest that such patients are at high risk of blood clots or stroke.

Anticlotting medications, or anticoagulants, are taken by patients who suffer from atrial fibrillation (irregular heartbeat) to reduce the risk of clots. Rivaroxaban, a novel anticoagulant, , has reached the market recently; having demonstrated its efficacy (as compared with traditional anticoagulant warfarin) in the ROCKET AF clinical trial. The benefits of rivaroxaban, compared with warfarin, are that it is taken once-daily and does not require the constant dose-adjustment monitoring of warfarin. However, there were concerns about the safety of rivaroxaban after administration is halted.

This new research aimed to investigate this risk, comparing the risk of subsequent blood clots/stroke in patients who stop taking rivaroxaban versus warfarin. The team investigated the incidence of such events following temporary interruptions and between 3–30 days after early drug discontinuation. Their findings indicated that both drugs had comparable outcomes, with risk of blood clots/stroke increasing after drug discontinuation.

The research was funded by the Duke Clinical Research Institute, Johnson & Johnson and Bayer HealthCare AG, and lead by Manesh Patel (Duke University School of Medicine, Durham, NC, USA). As Patel explains, unfortunately there is no obvious answer to rectify this problem: "No matter what drug they are on, patients who need anticoagulation revert back to their intrinsic risk of stroke or embolism after discontinuation, so it shouldn't be done lightly. Unfortunately, it's unclear how to provide optimal anticoagulation coverage during periods of transition."

– Written by Alice O'Hare

Source: American Heart Association press release. www.newsroom.heart.org/pr/aha/stroke-risk-high-when-anticlotting-232260.aspx

Recent study presents effect of daily aspirin on cancer metastasis risk

In a recent publication, UK scientists suggest daily aspirin could help in the treatment of some cancers.

In a paper published in a recent edition of *The Lancet*, a group of scientists from Oxford University (UK) have carried out a meta-analysis on five large trials on daily aspirin to discover any possible effects the drug may have on cancer metastasis.

The team, lead by Peter Rothwell of the Stroke Prevention Research Unit, Nuffield Department of Clinical Neuroscience (University of Oxford, UK) analyzed both paper and electronic records for patients who were diagnosed with cancer during these five UK trials. All five trials were studying the affect of aspirin on the prevention of vascular events.

A total of 987 out of 17,285 trial participants had a new solid cancer diagnosed during trial follow-up (representing approximately 6.5 years after the trials began). By studying these patients' records for tumor histology and clinical characteristics, the team could draw certain conclusions about how daily aspirin administration may affect tumor progression – more specifically the frequency of distant metastasis.

"By studying these patients' records for tumor histology and clinical characteristics, the team could draw certain conclusions about how daily aspirin administration may affect tumor progression..."

A reduction in cancer deaths was found in participants of the daily aspirin trials versus a control group. The research team hypothesizes that this could be due to aspirin preventing distant metastasis; and therefore they suggest aspirin could play a role in cancer treatment. As they state in their abstract: "This finding suggests that aspirin might help treatment of some cancers and provides proof-of-principle for pharmacological intervention specifically to prevent distant metastasis."

– Written by Alice O'Hare

Source: Rothwell RM, Wilson M, Price JF, Belch JFF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* 379(9826), 1591–1601 (2012).

The editorial team welcomes suggestions for timely, relevant items for inclusion in the news. If you have newsworthy information, please contact:
Cara Sutton,
Managing Commissioning Editor, *Clinical Investigation*
Tel.: +44 (0)20 8371 6090;
E-mail: c.sutton@future-science.com