Brothers in arms

Military funding for basic and applied biomedical science is thriving, with civilian applications delivered along the way

Andrea Rinaldi

War is the father of all things, Heraclitus believed. The military's demand for better weapons and transportation, as well as tools for communication, detection and surveillance has driven technological progress during the past 150 years or so, producing countless civilian applications as a fallout. The military has invested heavily into high-energy physics, materials science, navigation systems and cryptology. Similarly, military-funded biomedical research encompasses the whole range from basic to applied research programmes (Fig 1), and the portion of military-funded research in the biological and medical fields is now considerable.

...military-funded biomedical research encompasses the whole range from basic to applied research programmes...

War has always driven medical advances. From ancient Roman to modern times, treating the wounds of war has yielded surgical innovations that have been adopted by mainstream medicine. For example, the terrible effect of modern artillery on soldiers in the First World War was a major impetus for plastic surgery. Similarly, microbiology has benefited from war and military research: from antiseptics to prevent and cure gangrene to the massive production of penicillin during the Second World War, as well as more basic research into a wide range of pathogens, militaries worldwide have long been enthusiastic sponsors of microbiology research. Nowadays, military-funded research on pathogens uses state-of-the-art genotyping methods to study outbreaks

and the spread of infection and seeks new ways to combat antibiotic resistance that afflicts both combatants and civilians.

The US Military Infectious Diseases Research Program (MIDRP) is particularly active in vaccine development to protect soldiers, especially those deployed overseas. Its website notes that: "Since the passing of the 1962 Kefauver–Harris Drug Amendment, which added the FDA requirement for proof of efficacy in addition to proof of safety for human products, there have been 28 innovative vaccines licenced in the US, including 13 vaccines currently designated for paediatric use. These 28 innovative vaccine products targeted new microorganisms, utilized new technology, or consisted of novel combinations of vaccines. Of these 28, the US military played a significant role in the development of seven licenced vaccines" (<https://midrp.amedd.army.mil/>). These successes include tetravalent meningococcal vaccine and oral typhoid vaccine, while current research is looking into the development of vaccines against malaria, dengue fever and hepatitis E.

Similarly, the US Military HIV Research Program (MHRP) is working on the development of a global HIV-1 vaccine (<http://www.hivresearch.org>). MHRP scientists were behind the RV144 vaccine study in Thailand—the largest ever HIV vaccine study conducted in humans—that demonstrated that the vaccine was capable of

...military-funded research on pathogens uses state-of-the-art genotyping methods to study outbreaks and the spread of infection

The treatment of wounds, shock and the rehabilitation of major trauma patients are the very essence of medical aid on the battlefield

eliciting modest and transient protection against the virus [1]. In the wake of the cautious optimism raised by the trial, subsequent research is providing insights into the workings of RV144 and is opening new doors for vaccine designers to strengthen the vaccine. In a recent study, researchers isolated four monoclonal antibodies induced by the RV144 vaccine and directed at a particular region of the HIV virus envelope associated with reduced infection, the variable region 2. They found that these antibodies recognized HIV-1-infected CD4(+) T cells and tagged them for attack by the immune system [2].

In response to the medical problems military personnel are suffering in Iraq and Afghanistan, a recent clinical trial funded by the US Department of the Army demonstrated the efficacy of the aminoglycoside antibiotic paromomycin—either with or without gentamicin—for the topical treatment of cutaneous leishmaniasis, the most common form of infection by *Leishmania* parasites. Cutaneous leishmaniasis—which is endemic in Iraq and Afghanistan and rather frequent among soldiers deployed there—is transmitted to humans through the bite of infected sandflies: it causes skin ulcers and sores and can cause serious disability and social prejudice [3]. Topical treatments would offer advantages over therapies that require the systemic administration of antiparasitic drugs. The study—a phase 3 trial—was conducted in Tunisia and

enrolled some 375 patients with one to five ulcerative lesions from cutaneous leishmaniasis. Patients, all aged between 5 and 65, received topical applications of a cream containing either 15% paromomycin with 0.5% gentamicin, 15% paromomycin alone or the control cream, which contained no antibiotic. The combination of paromomycin and gentamicin cured cutaneous leishmaniasis with an efficacy of 81%, compared with 82% for paromomycin alone and just 58% for control—the skin sores of cutaneous leishmaniasis often heal on their own. Researchers reported no adverse reactions to paromomycin-containing creams. Because the combination therapy with gentamicin is probably effective against a larger range of *Leishmania* parasitic species and strains causing the disease, it could become a first-line treatment for cutaneous leishmaniasis on a global scale the authors concluded [3].

Not surprisingly, trauma and regenerative and reconstructive medicine are other large areas of research in which military influence is prevalent. The treatment of wounds, shock and the rehabilitation of major trauma patients are the very essence of medical aid on the battlefield (Figs 2,3). “Our experience of military conflict, in particular the medicine required to deal with severe injuries, has led to significant improvements in trauma medicine. Through advances in the prevention of blood loss and the treatment of coagulopathy for example, patients are now surviving injuries that 5–10 years ago would have been fatal,” said Professor Janet Lord, who leads a team investigating the inflammatory response in injured soldiers at the National Institute for Health Research Surgical Reconstruction and Microbiology Research Centre (NIHR SRMRC) in Birmingham, UK (<http://www.srmrc.nihr.ac.uk/>).

NIHR SRMRC integrates basic researchers at Birmingham University with clinicians and surgeons at the Royal Centre for Defence Medicine and University Hospital Birmingham to improve the treatment of traumatic injury in both military and civilian patients. As Lord explained, the centre has two trauma-related themes. The first is looking at, “[t]he acute response to injury, which analyses the kinetics and nature of the inflammatory response to tissue damage and is developing novel therapies to ensure the body responds appropriately to injury and does not stay in a hyper-inflamed

This could be your boy or your pal

Your Pint of Blood Might Save His Life. Blood defeats death! On scores of battle fronts, precious blood—given from a heart-felt desire to serve—is routing pain and shock and utter exhaustion. Blood is the magic fluid of life. It is your privilege to give it—*here and now*. This is your part to play, that your boy—your Pal, may live.

Do your blood-bit, and thus help to prolong useful vital lives through their natural span. This is the debt of gratitude of us all, to the boys in uniform. Only our own life blood can buoy the life flame of the grievously wounded. So, give of your blood, that men may live and that a better, freer world may be assured.

Here at Diebold, we all are 100% behind the war effort. We give of our time, our energy, our prayers. But, we back these efforts by buying war bonds, and by giving generously of our vital life blood. We are so proud, thus to serve.

DIEBOLD, INCORPORATED
CANTON 2, OHIO

DIEBOLD ARMOR
FOR AMERICAN ARMED FORCES

BUY WAR BONDS!

DIEBOLD

Systems to Fit the Routine

CARDINEER ROTARY FILES	TRA-DEX VERTICAL VISIBLE FILES	FLEX-SITE VISIBLE BOOK
---------------------------	-----------------------------------	---------------------------

Ready for immediate delivery

Available when victory comes—Sales; Money Chests; Electric Rickshaws; Bank Vaults; Office Accessories

Fig 1 | 1944 advertisement for Diebold Inc. (Ohio, USA) in support of blood donations for soldiers wounded in the Second World War. The military has traditionally been one of the greatest proponents of active research on synthetic blood production, blood substitutes and oxygen therapeutics for treating battlefield casualties. One recent approach in this direction is The Defense Advanced Research Projects Agency's (DARPA's) Blood Pharming programme, which plans to use human haematopoietic stem cells—such as those obtained from umbilical cord blood—as a “starting material to develop an automated, fieldable cell culture and packaging system capable of producing transfusable amounts of universal donor red blood cells” (http://www.darpa.mil/Our_Work/DSO/Programs/Blood_Pharming.aspx).

state. The latter is a particular issue with older patients whose chance of recovery from trauma is significantly lower than younger patients,” she said. The second theme is, “[n]eurotrauma and regeneration, which studies traumatic brain injury, trying to develop better ways to detect this early to prevent poor outcomes if it goes undiagnosed,” Lord said.

Kevlar helmets and body armour have saved the lives of many soldiers, but they

do not protect much the face and eyes, and in general against blasts to the head. Because human retinas and brains show little potential for regeneration, patients with face and eye injuries often suffer from loss of vision and other consequences for the rest of their lives. However, a new stem cell and regenerative approach for the treatment of retinal injury and blindness is on the horizon. “Recent progress in stem cell research has begun to emerge on the

possible exploitation of stem cell-based strategies to repair the damaged CNS (central nervous system). In particular, research from our laboratory and others have demonstrated that Müller cells—dormant stem-like cells found throughout the retina—can

serve as a source of retinal progenitor cells to regenerate photoreceptors as well as all other types of retinal neurons,” explained Dong Feng Chen at the Schepens Eye Research Institute, Massachusetts Eye and Ear of the Harvard Medical School in

Boston (Massachusetts, USA). In collaboration with the US Department of Defence, the Schepens Institute is steering the Military Vision Research Program, “to develop new ways to save the vision of soldiers injured on today’s battlefield and to push the frontier of vision technologies forward” (<http://www.schepens.harvard.edu>).

“My laboratory has shown that adult human and mouse Müller cells can not only regenerate retina-specific neurons, but can also do so following induction by a single small molecule compound, alpha-amino adipate,” Chen explained. She said that alpha-amino adipate causes isolated Müller glial cells in culture to lose their glial phenotype, express progenitor cell markers and divide. Injection of alpha-amino adipate into the subretinal space of adult mice *in vivo* induces mature Müller glia to de-differentiate and generate new retinal neurons and photoreceptor cells [4]. “Our current effort seeks to further elucidate the molecular pathways underlying the regenerative behaviour of Müller cells and to achieve functional regeneration of the damaged retina with small molecule compounds,” Chen said. “As the retina has long served as a model of the CNS, and Müller cells share commonalities with astroglial lineage cells in the brain and spinal cord, the results of this study can potentially be broadened to future development of treatment strategies for other neurodegenerative diseases, such as brain and spinal cord trauma, or Alzheimer and Parkinson disease.”

Brain injuries account for a large percentage of the wounds sustained by soldiers. The Defense Advanced Research Projects Agency (DARPA), an agency of the US Department of Defense, recently awarded US\$6 million to a team of researchers to develop nanotechnology therapies for the treatment of traumatic brain injury and associated infections. The researchers are trying to develop nanoparticles carrying small interfering RNA (siRNA) molecules to reach and treat drug-resistant bacteria and inflammatory cells in the brain. Protecting the siRNA within a nanocomplex covered with specific tissue homing and cell-penetrating peptides will make it possible to deliver the therapeutics to infected cells beyond the blood–brain barrier—which normally makes it difficult to get antibiotics to the brain. The project has been funded within the framework of DARPA’s *In Vivo* Nanoplatforms programme that “seeks to develop new classes

Fig 2 | Medical services in Britain, 1917. Making an artificial leg for a wounded serviceman at Roehampton Hospital in Surrey. This image is from The First World War Poetry Digital Archive, University of Oxford (www.oucs.ox.ac.uk/ww1lit). Copyright: The Imperial War Museum.

Fig 3 | US soldiers use the fireman’s carry to move a simulated casualty to safety during a hyper-realistic training environment, known as trauma lanes, as part of the final phase of the Combat Lifesaver Course given by medics from Headquarters Support Company, Headquarters and Headquarters Battalion, 25th Inf. Div., USD-C, at Camp Liberty, Iraq, March 2011. Credit: US Army, photo by Sgt Jennifer Sardam.

of adaptable nanoparticles for persistent, distributed, unobtrusive physiologic and environmental sensing as well as the treatment of physiologic abnormalities, illness and infectious disease" (www.darpa.mil).

"The DARPA funding agency often uses the term 'DARPA-hard' to refer to problems that are extremely tough to solve. What makes this a DARPA-hard problem is the fact that it is so difficult to deliver therapeutics to the brain. This is an underserved area of research," explained team leader Michael Sailor, from the University of California San Diego, in a press release (http://ucsdnews.ucsd.edu/pressrelease/darpa_awards_6_million_to_develop_nanotech_therapies_for_traumatic_brain_in).

In the near future, DARPA, whose budget is set for a 1.8% increase to US\$2.9 billion next year, will focus on another important project dealing with the CNS. The BRAIN Initiative—short for Brain Research through Advancing Innovative Neurotechnologies—is a new research effort whose proponents intend will "revolutionize our understanding of the human mind and uncover new ways to treat, prevent, and cure brain disorders like Alzheimer's, schizophrenia, autism, epilepsy and traumatic brain injury" (www.whitehouse.gov). Out of a total US\$110 million investment, DARPA will obtain US\$50 million to work on understanding the dynamic functions of the brain and demonstrating breakthrough applications based on these insights (Fig 4). In addition to exploring new research areas, this money will be directed towards ongoing projects of typical—although not exclusive—military interest that involve enhancing or recovering brain functions, such as the development of brain-interfaced prosthetics and uncovering the mechanisms underlying neural reorganization and plasticity to accelerate injury recovery.

"[T]here is this enormous mystery waiting to be unlocked, and the BRAIN Initiative will change that by giving scientists the tools they need to get a dynamic picture of the brain in action and better understand how we think and how we learn and how we remember. And that knowledge could be—will be—transformative," said US President Obama, presenting the initiative (<http://www.whitehouse.gov/the-press-office/2013/04/02/remarks-president-brain-initiative-and-american-innovation>).

"The President's initiative reinforces the significance of understanding how the brain

Fig 4 | The BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative infographic. A complete version can be downloaded at <http://www.whitehouse.gov/infographics/brain-initiative>.

records, processes, uses, stores and retrieves vast quantities of information. This kind of knowledge of brain function could inspire the design of a new generation of information processing systems; lead to insights into brain injury and recovery mechanisms; and enable new diagnostics, therapies and devices to repair traumatic injury," explained DARPA Director Arati Prabhakar in a press release (<http://www.darpa.mil/NewsEvents/Releases/2013/04/02.aspx>).

But BRAIN is also stirring up some controversy. Some scientists fear that this kind of 'big and bold' science, with a rigid top-down approach and vaguely defined objectives, will drain resources from smaller projects in fundamental biology [5]. Others ask whether

the BRAIN project investment will really generate the huge return hinted at in Obama's speech during the initiative's launch, or whether a substantial amount of hype about the potential outcomes was used to sell the project (<http://ksj.mit.edu/tracker/2013/04/obamas-brain-initiative-and-alleged-140>).

As these examples show, the most important player in military-funded biomedical research is the USA, with the UK following at a distance. But other countries with huge defence budgets are gearing up, although with less visibility. In July 2011, for instance, India and Kyrgyzstan opened the joint Mountain Biomedical Research Centre at the Kyrgyz

capital Bishkek, to carry out research into the mechanisms of short- and long-term high-altitude adaptation. The institute will use molecular biological approaches to identify markers for screening people for high-altitude resistance and susceptibility to high-altitude sickness, and development of other mountain maladies. On the Indian side, the scientists involved in the new research centre belong to the Defence Institute of Physiology and Applied Sciences, and the money came from India's defence budget.

As mankind seems unlikely to give up on armed conflicts anytime soon, war-torn human bodies will still need to be cured and

wounds healed. Whether the original impetus for military-funded biomedical research is noble or not, it nonetheless fuels considerable innovation leading to important medical discoveries that ultimately benefit all.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

REFERENCES

1. Rerks-Ngarm S *et al* (2009) Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* **361**: 2209–2220
2. Liao HX *et al* (2013) Vaccine induction of antibodies against a structurally heterogeneous site of immune pressure within HIV-1 envelope protein variable regions 1 and 2. *Immunity* **38**: 176–186
3. Ben Salah A *et al* (2013) Topical paromomycin with or without gentamicin for cutaneous leishmaniasis. *N Engl J Med* **368**: 524–532
4. Takeda M, Takamiya A, Jiao JW, Cho KS, Trevino SG, Matsuda T, Chen DF (2008) alpha-Aminoadipate induces progenitor cell properties of Müller glia in adult mice. *Invest Ophthalmol Vis Science* **49**: 1142–1150
5. Wadman M (2013) Behind the scenes of a brain-mapping moon shot. *Nature* **495**: 19

Andrea Rinaldi is a freelance science writer in Cagliari, Italy.

EMBO reports (2013) **14**, 866–870; published online 13 September 2013; doi:10.1038/embo.2013.146