A cute radiation syndrome (ARS) is the result of a radiation overdose to the body—a particularly common after-effect of nuclear war, terrorist attacks or nuclear accidents. It can lead to the life-threatening destruction of stem cells in the bone marrow which play a vital role in producing important blood cells. The last two decades have seen breakthroughs in the field of stem cell research and, as such, stem cells can now be generated artificially in the laboratory. This next big challenge is to leverage existing knowledge to develop stem cell-based therapies for diseases caused by abnormalities in the bone marrow. The consortium from the Institute for Radiological Protection and Nuclear Safety (IRSN) and National Institute of Health and Medical Research (INSERM) is striving to achieve just that, having already made great advances in producing blood artificially—this team were the first to produce functional human blood from skin cells in vivo.

SOCIAL, ECONOMIC, ENVIRONMENTAL, AND INDUSTRIAL CHALLENGES

ARS is often a result of one of five key events. These include: exposure to a nuclear explosion, a nuclear reactor accident, an accident when handling fissile materials, exposure to a powerful beamwidth, or an act of terrorism. ARS was responsible for 380 deaths between 1945 and 2004 from 600 identified radiological accidents—excluding Hiroshima and Nagasaki. A nuclear accident in Chernobyl in 1986 caused over two hundred workers and firefighters to suffer ARS. This event proves that, despite nuclear safety precautions being put in place, nuclear accidents can still happen—and they can be devastating when they do. At present, 442 nuclear power reactors are operating in 31 countries, with sixty-five further nuclear reactors under construction. Not only that, but numerous nuclear reactors can also be found on military warships—once again demonstrating why the risk of nuclear accidents occurring remains such a major concern for military agencies. Developing and implementing a therapeutic strategy capable of dealing with the radiative effects of nuclear accidents or terrorist attacks, is therefore vital for both military operatives and civilian populations.

ACUTE RADIATION SYNDROME

The European Commission has formed a consortium of experts to develop a manual of medical care following accidental irradiation. This will, in effect, develop a system for assessing organ damage in relation to the time following the accident and classifying this using prognostic codes for the neurovascular, haematopoietic, cutaneous and gastrointestinal systems. The extent of this accidental irradiation can often be diverse but in the most severe cases stem cell transplants should be considered as a therapeutic option. Currently however, and due to the nature of the incident in which the irradiation occurred (i.e., nuclear accident or terrorist attack), accessing large stocks of stem cells for victims proves difficult. As such, there remains a gap in the management of acute radiation syndrome. The consortium are investigating a new therapeutic approach to bridge this gap and ensure help is available when needed.

BEYOND ACUTE RADIATION SYNDROME

Chemotherapy in leukaemia patients is, in a way, a voluntary exposure to damageous doses of radiation. The aim is to destroy cancerous cells in the patient’s bone marrow to subsequently replace them with healthy haematopoietic blood-cell producing stem cells (HSCS) either from the patient themselves or from a healthy donor. Haematopoietic stem cell transplantation has become the main treatment used in the management of various haematologic malignancies, but it is not without its issues. In the European Union alone, over 5000 individuals per year receive HSC transplants for haematological diseases and malignancies. However, significant numbers of patients (20-30%) cannot receive the life-saving treatment they require because they cannot access sufficient numbers of HLA-matched HSCs (this kind of matching uses a protein, human leukocyte antigen, located on the body’s cells—it acts as an indicator to your immune system that your cells belong). Not only that, but treatments often fail due to the matched donor cell not being well-enough suited, resulting in graft vs host disease (GVHD). In other words, even though donors are carefully matched to maximise the chances of acceptance, graft rejection is common when using donor cells. GVHD contributes substantially to transplant-related morbidity and mortality. A perfect donor match can only be achieved by using the patient’s own stem cells. This bears the risk that the disease returns because of residual diseased cells in the graft. Nonetheless, haematopoietic stem and progenitor cells, generated from patient-derived induced pluripotent stem cells (iPSC), could provide an unlimited supply of HLA-matched transplantable cells capable of treating disease. In 2006, researchers at Kyoto University in Japan identified one of treating disease. In 2006, researchers at Kyoto University in Japan identified one of the first to develop induced pluripotent stem cells (iPSC), contributing substantially to transplant-related morbidity and mortality.

Stem cell therapy: the answer to radiation damage

The team of scientists at the Institute for Radiological Protection and Nuclear Safety (IRSN) and National Institute of Health and Medical Research (INSERM) aim to develop novel cell therapies for tissue damage caused by radiation. In their latest research, the GIPSIS project, the team investigates the potential of using cutting-edge stem cell therapy to produce important blood cells. The last two decades have seen breakthroughs in the field of stem cell research and, as such, stem cells can now be generated artificially in the laboratory. This next big challenge is to leverage existing knowledge to develop stem cell-based therapies for diseases caused by abnormalities in the bone marrow. The consortium from the Institute for Radiological Protection and Nuclear Safety (IRSN) and National Institute of Health and Medical Research (INSERM) is striving to achieve just that, having already made great advances in...

Acute radiation syndrome is the result of a radiation overdose to the body—a particularly common after-effect of nuclear war, terrorist attacks or nuclear accidents...
Why are patient fibroblasts not damaged by acute radiation? Because radiation may damage DNA introducing mutations. In cases of accidental irradiation, there is a small part of the exposed victim which is not irradiated. So, first we determine which part of the body has not been irradiated, then we take a small biopsy of skin in order to produce iPSCs after carefully checking that there is no DNA damage.

How long will the GIPSIS project take? These years (2014-2017) it will be followed by another project (2017-2020) in order to produce clinical grade cells. The next project will run from 2017 to 2020.

What are the most important quality criteria for a clinical-grade cell therapy? We are establishing protocols for generating of human induced pluripotent stem cells (hPSCs) that would not involve viral vector integration, and that are compatible with Good Manufacturing Practices (GMP) standards: no integrative reprogramming, clone selection, absence of mutations on 50 hot spots, GMP, graft without contamination of iPSC, biodistribution to long-term in animal and absence of teratoma, production of cells by a labelled cell therapy unit.

**Research Objectives**

IRSN’s research looks at using haematopoietic stem cell therapy to improve the medical management of acute radiation syndrome (ARS) for members of the human and the public who have been victims of nuclear accidents and exposure.

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**BIO**

For 25 years, Dr Alain Chapel has been developing gene and cell therapy using non-human primates, immune-tolerant mice and rats to protect against the side effects of radiation. He collaborates with clinicians to develop strategies for treatment of patients after radiotherapy exposures.

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