Cluster 5: Health Care - Report

CLUSTER 5

March 2012

The THESEUS Coordination and Support Action has received funding from the European Community's 7th Framework Programme (FP7/2007-2013) under grant agreement n°242482.

Towards Human Exploration of Space: a EUropean Strategy

Cluster 5: Health Care - Report

Space Medicine

Medication in space

THESEUS: Towards Human Exploration of Space – a European Strategy

Past space missions in low Earth orbit have demonstrated that human beings can survive and work in space for long durations. However, there are pending technological, medical and psychological issues that must be solved before adventuring into longer-duration space missions (e.g. protection against ionizing radiation, psychological issues, behaviour and performance, prevention of bone loss, etc.). Furthermore, technological breakthroughs, e.g. in life support systems and recycling technologies, are required to reduce the cost of future expeditions to acceptable levels. Solving these issues will require scientific and technological breakthroughs in clinical and industrial applications, many of which will have relevance to health issues on Earth as well.

Despite existing ESA and NASA studies or roadmaps, Europe still lacks a roadmap for human exploration of space approved by the European scientific and industrial communities. The objective of THESEUS is to develop an integrated life sciences research roadmap enabling European human space exploration in synergy with the ESA strategy, taking advantage of the expertise available in Europe and identifying the potential of non-space applications and dual research and development.

THESEUS Expert Groups

The basis of this activity is the coordination of 14 disciplinary Expert Groups (EGs) composed of key European and international experts in their field. Particular attention has been given to ensure that complementary expertise is gathered in the EGs.

EGs are clustered according to their focus:

Cluster 1: Integrated Systems Physiology
Bone and muscle
Heart, lungs and kidneys
Immunology
Neurophysiology
Nutrition and metabolism

Cluster 2: Psychology and Human-machine Systems
Group/team processes
Human/machine interface
Skill maintenance

Cluster 3: Space Radiation
Radiation effects on humans
Radiation dosimetry

Cluster 4: Habitat Management
Microbiological quality control of the indoor environment in space
Life support: management and regeneration of air, water and food

Cluster 5: Health Care
Space medicine
Medication in space

Identification of Research Priorities and Development of the THESEUS Roadmap

Each Expert Group based their work on brainstorming sessions dedicated to identifying key issues in their specific field of knowledge. Key issues can be defined as disciplinary topics representing challenges for human space exploration, requiring further attention in the future. These key issues were addressed to the scientific community through an online consultation; comments and inputs received were used to refine them, to consider knowledge gaps and research needs associated to them, as well as to suggest potential investigations.

The outcomes and main findings of the 'Integrated Systems Physiology' EGs have been synthesised into this report and further integrated to create the THESEUS roadmap.

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1 Space Medicine

1.1. Introduction

The 'Space Medicine' Expert Group based its work on the evaluation of 35 issues that were identified as relevant for this area of expertise. Of the 35 issues, the group considered received from the community and came up with a list of 16 Key Issues of the highest priority, grouped into six overarching themes:

- Health maintenance
- Diagnostic procedures
- Health care delivery
- Medical education and skill maintenance
- On-board medical resource management
- Ethical, legal and moral considerations in space medicine

The priorities of research necessary to support foreseen space travel and planetary exploration represent a unique set of problems whose solution demands an in-depth understanding of the whole human body and cross disciplinary work between life scientists, engineers and technologists. All the necessary expertise has been acquired by European scientists during the past decades. In the context of the THESEUS project, the objective of this Expert Group was to gather this European expertise and create synergies, allowing an integrated approach on emerged priorities of research. Because of the necessary holistic approach, those research programmes obviously required the involvement of scientists whose expertise is disseminated across Europe.

The following sections present the conclusions the 'Space Medicine' Expert Group. This group met during two expert workshops in 2010. Those workshops were aimed at considering the key questions to address, the latest developments, the gaps to fill and the Earth-based applications.

The Expert Group recommends that key issues presented in this report are considered at their true value and addressed in future research programmes.

1.2. Health Maintenance – Key Issues

1.2.1. Key Issue 1: Insufficient control of infectious diseases, potentially exacerbated by on-board micro-organism mutations, drug inefficiencies and drug resistance - Provide an on-board available means to deal with the risk of infectious disease

The possibility of micro-organism mutation occurring as a result of the high radiation environment is not negligible. This presents a threat to the crew due to the possibility of increased incidence of infectious disease as a result of such mutations if adequate therapies are not available during an exploration mission, where the possibility of Earth return does not exist. Since the 1980s, the field of terrestrial healthcare has been engaged in a "permanent fight" against hospital-borne, resistant infections (nosocomial). The threat is still high and requires significant attention. Any progress in this field in the space medicine domain is very likely to have immediate applications to terrestrial heath care.

The following recommendations are made:

- Conduct a state of the art investigation (including the terrestrial healthcare domain, closed environments and space) with the collection of past data (i.e. conduct a data mining exercise).
- Provide the capability to prevent, monitor and treat infectious disease in-flight.
- Support R&D activities in real time in-situ bio-monitoring for all potential infectious organisms.
- Support R&D activities in the elimination and/or control of all potentially infectious organisms.
- Support R&D activities in the treatment of harmful effects caused by infectious organisms.

Interdisciplinary aspects

For the mutations aspects, links with radio-biology and infection medication efficiency in space are comprehensive.

Figure 1: Surface, Water and Air Bio-characterisation (SWAB Experiment) on-board the ISS (Credit: NASA)

1.2.2. Key Issue 2: the acute risk to health from radiation exposure, in particular solar flares - Provide on-board physical and/or pharmacological countermeasures and/or protection

The possibility of acute exposure to radiation from solar flares will be a permanent threat to crew during exploration missions. Little progress has been made in the last decade in the field of acute exposure to ionising radiation therapy. Any progress in this domain will be directly applicable to terrestrial radio-therapy domains, in particular for the treatment of cancer.

The following recommendations are made:

- Conduct a state of the art investigation (data mining) in the field.
- Provide the capability to monitor, predict, prevent and treat exposure to the effects of solar flares.
- Support R&D activities for real time in-situ bio-dosimetry.
- Support R&D activities that may predict acute cosmic radiation events.
- Support R&D activities that may prevent or reduce the effects of acute and chronic radiation.
- Support R&D activities in the treatment and management of acute and chronic radiation effects.
- More accurately define radiation effects and radiation limits as well as ethical constraints.

Interdisciplinary aspects

Clear links exist with the radiation-biology and radiation-protection domains, in particular with respect to hazardous environment operations such as working with nuclear reactors or on-board nuclear vehicles (e.g. submarines).

1.2.3. Key Issue 3: dietary and nutrition-related space flight disorders and complaints - Provide on-board countermeasures

The dietary regime should not contribute to health disorders induced by micro-gravity. The unavailability of fresh food, and thus monotony of preserved foods, will be a dominant crew experience during Earth – planet transfer periods. Consequently, particular care must be applied to crew nutrition and dietary considerations. Presently, several dietary studies are being conducted on the ISS and during space mission simulations. These are focussed on improving knowledge of the effects of salt load on the body and bone related factors, such as Vitamin D.

The following recommendation is made:

- Support R&D activities to improve the availability and palatability of "fresh" and preserved food for long periods to prevent nutritional disorders. *(Assumption: food is delivered in appropriate nutrient mix).*

Interdisciplinary aspects

There are clear links with the domains of physiology, psychology and behaviour. Research progress in support of the above mentioned space issues will improve knowledge on the interaction of diet and health in terrestrial circumstances as well, in particular with regards to the effects of high sodium load on human health and improved means to maintain bone.

1.2.4. Key Issue 4: sub-optimal physical countermeasure hardware for health maintenance - Identify and provide improved solutions to current bone and muscle loss countermeasures

Micro-gravity induced bone and muscle loss seen in the lower body is an unresolved aspect of human spaceflight. Crew undertaking long term exploration missions will face this problem, which if not countered successfully, will have operational consequences. Mastering these problems remains one of the highest priorities for human exploration missions. At the present time, a number of studies concerning bone and muscle loss are being (or are planned to be) conducted on the ISS and during bed rest studies.

The following recommendations are made:

- Advocate the use of artificial gravity and support R&D activities investigating its use.
- Support R&D activities investigating integrated countermeasure systems which positively affect multiple physiological systems, and which may include the combination of mechanical and pharmaceutical systems.

Interdisciplinary aspects

There are clear links with the domain of physiology, in particular in relation to bone, muscle and exercise capacity. For the condition of osteoporosis, improved knowledge of the mechanical factors concerning bone remodelling will augment the prevention and treatment for terrestrial sufferers. Human spaceflight research has already contributed to a better understanding, but additionally will contribute to identification and development of better countermeasures to prevent osteoporosis, bone loss and muscle atrophy.

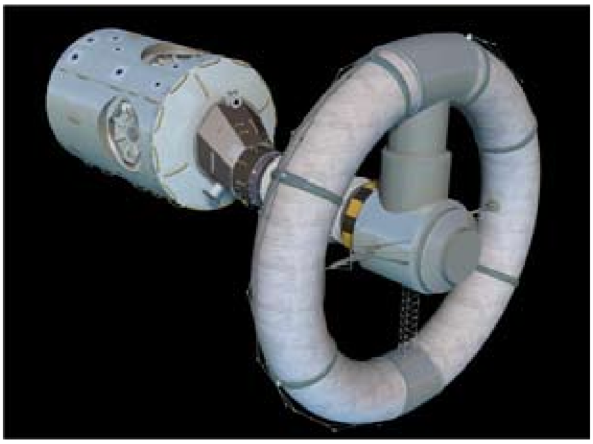

Figure 2: Concept of centrifuge on-board ISS (Credit: NASA)

1.3. Diagnostic Procedures – Key Issues

1.3.1. Key issue 5: Insufficient on-board medical imaging hardware - Provide on-board means to maintain medical risks at an acceptable level

The need for user-friendly medical imaging devices in-flight is mandatory, however, it is difficult to anticipate (other than for ultrasound) what will be available for use within the next decade or two. This need has been considered to be at the highest priority level because of its criticality. Compact and portable digital X-Ray equipment is already in existence, capable of auto-diagnostic and 3D imaging, and the provision of an expert system for the diagnosis of bone mineral density disorders.

Figure 3: Ultra-sound eye imaging on-board ISS (Credit: NASA)

The following recommendations are made (they assume that efficient on-board imaging techniques will be absolutely necessary):

- Support R&D activities to develop user friendly imaging techniques for trained operators.
- Support R&D activities to develop layman useable imaging techniques with the following characteristics (note: these techniques will also be useful for research) :
    - Auto-diagnosis
    - Real-time use
    - True-life fidelity
    - 3D imaging

Interdisciplinary aspects

Links with other disciplines exist (medical e.g. bone loss, national security e.g. counter-terrorist, disaster relief e.g. survivor triage), however, to date it is mainly a space medicine concern.

1.3.2. Key issue 6: Insufficient on-board smart sensors / smart devices for health monitoring & medical diagnostics. - Provide on-board means to maintain medical risks at an acceptable level.

Continuous medical monitoring is necessary due to the inevitable high risk activities that will be conducted during human exploration missions. This monitoring should not disturb the crew in any form, and thus the use of smart body sensors within clothing and environmental sensors within (and external to) the habitable volume will be required. In the last decade, the European Commission has supported research concerning smart sensors.

The following recommendation is made:

- Support R&D activities in the development of smart and advanced sensors and devices for the measurement and intelligent analysis of multiple physiological and environmental parameters:
- Human standpoint: invasive and non-invasive,
- Habitat standpoint: internal and external.

Interdisciplinary aspects

There are not many obvious links with other disciplines as this is primarily a space-related issue, however, progress in this field will lead to a smart monitoring capability for high risk professions and persons in hostile environments.

1.3.3. Key issue 7: Insufficient on-board expert systems / decision support systems for medical diagnostics. - Provide on-board means to maintain medical risk at an acceptable level.

For exploration missions, the crew will need to be as autonomous as possible for medical issues. On-board expert systems will be required to support this capability. ESA has been supporting developments in the domain of augmented reality since 2009.

The following recommendations are made:

- Conduct a state of the art investigation into existing and expected medical expert systems.
- Support R&D activities to develop next generation medical expert systems that:
- Aid the prevention (including detection) of harmful medical conditions
- Aid the diagnosis of medical conditions
- Support the treatment of medical conditions
- Support and optimise the management of available medical resources
- Enable physician's skill maintenance

Interdisciplinary aspects

There are clear links with many other health care disciplines because medical expert systems such as these will be useful for everyday medical practices on Earth.

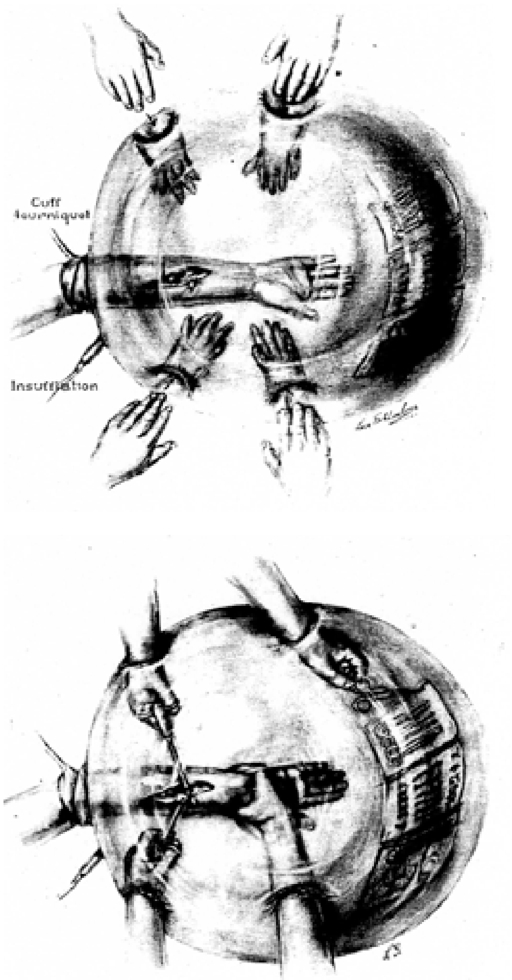

Figure 4: Possible 0-g surgical glove box (Credit: NASA)

1.3.4. Key issue 8: Insufficient on-board drugs for medical/surgical procedures. - Provide the capability to offer sufficient drugs and appropriate procedures to maintain on-board medical risks at an acceptable level.

This is a key issue of the highest priority for space medicine operations during manned space exploration missions. For details of relevance, latest developments, Earth benefits and applications, see the report from THESEUS "Medication in Space" expert group.

1.3.5. Key issue 9: Insufficient on-board equipment to make sufficient medical procedures available for appropriate health care delivery. - Provide on-board capability to maintain medical risks at an acceptable level.

This is a key issue of the highest priority for space medicine operations during human space exploration. The health care technology field is a domain that continually progresses and evolves.

Considering the long time before the actual development of a human space exploration mission,

the following recommendations are made:

- Support the development and update of risk assessment protocols that can be used to enable the identification of medical equipment and procedures required for exploration.
- Support R&D activities in microgravity compatible medical equipment and procedures.

Figure 5: ISS Crew Restraint System (Credit: NASA)

Interdisciplinary aspects

Links with other disciplines and Earth applications are for example: emergency preparedness for terrestrial expeditions, military operations and small group, isolation and confinement activities.

1.3.6. Key issue 10: Insufficient on-board surgical techniques and devices (e.g. endoscopic procedures, restraint systems etc.) - Provide sufficient on-board surgical techniques and devices to maintain medical risks at an acceptable level.

This is an open issue for space medicine operations required for human space exploration missions. The health care technology field is a domain that continually progresses and evolves.
Considering the long time before implementing the development of human space exploration missions,

the following recommendations are made:

- Support the development and update of risk assessment protocols to be used to enable the identification of the surgical techniques and devices required for exploration.
- Support R&D activities in to microgravity compatible surgical techniques and devices.

Interdisciplinary aspects

Links exist with other disciplines, however, there is little cross over with terrestrial healthcare except for situations where small groups are required to exist in long duration confinement circumstances.

1.4. Medical Education and Skill Maintenance – Key Issues

Figure 6: Surgery Trainer (Credit: Ohio Supercomputer Center)

1.4.1. Key issue 11: Insufficient provision of virtual reality training systems/human patient simulators. - Provide on-board capability to maintain medical risks at an acceptable level during human exploration missions.

The maintenance of on-board medical skills is an issue of the highest priority for space medicine operations for human space exploration missions. The field of electronic training is presently in a state of exponential growth, promising to produce highly useful and effective tools in the near future.

The following recommendation is made:

- Support the development of virtual techniques, systems and simulators for the maintenance of medical skills, treatment and crew education.

Interdisciplinary aspects

Links exist with other disciplines where skill maintenance in an isolated environment is required. With the exception of small group isolation/confinement activities, there are few terrestrial operational applications, however, advances in e-skills training may be applied in many industries to reduce the need for direct expert lead training.

1.4.2. Key issue 12: Lack of provision of appropriate medical curricula for physician astronauts. - Provide capability to achieve and maintain physician skill sets and knowledge to maintain medical risks at an "acceptable" level during human exploration missions.

The provision of space medicine-specific academic curricula is an issue of high priority for space medicine operations in preparation for human space exploration missions, to ensure on-board medical knowledge is appropriate. The domain of medical training is constantly evolving and will continue to do so.

The following recommendation is made:

- Support the identification and development of space-health specific curricula which include physical, psychological and social elements in relation to mission scenarios/constraints.

Interdisciplinary aspects

Links exists between this domain and other terrestrial human medical specialities where space specific academic content is relevant e.g. baro-medicine, disuse atrophy.

1.5. On-Board Medical Resource Management – Key Issue

1.5.1. Key issue 13: Lack of provision of methods to define the minimum on-board medical infrastructure needed to maintain medical risks at an "acceptable" level during human exploration missions.

This is a key issue of high priority for future space medicine operations. The methods defined shall be coherent with exploration mission safety objectives where medical issues will be but one aspect of risk among others. The current approach is the probabilistic risk assessment method; an evolution of this method or new forms of risk assessment will be required.

The following recommendation is made:

- Support the development of updated risk assessment methods and associated mitigation strategies to be used prior to the finalisation of exploratory mission design and associated infrastructure.

Interdisciplinary aspects

Many links are possible with other human activities where risk and its mitigation is of concern. The risk assessment models will be applicable to various aspects of space missions but also to terrestrial endeavours such as military operations, expeditions and extreme environment resource acquisition (e.g. oil rig operations).
Due to the limitations of health care delivery and diagnostics capabilities which are below terrestrial standards, an adaptation of ethical, legal and moral norms is required for human space exploration.

1.6. Ethical, Legal and Moral Considerations in Space Medicine –Key Issues

1.6.1. Key issue 14: What triage decisions and medical capability limitations shall be acceptable during human exploration missions?

This is a key issue of high priority for space medicine operations. These considerations shall be coherent with international ethical practice and mission safety objectives. Ethical practice is under continual debate.

The following recommendations are made:

- Encourage the international discussion, debate and knowledge exchange on human exploration mission related ethical decisions
- Support the development of ethical and medical flight guidelines and rules
- Support the development of adequate training for the conduct of medical flight guidelines, rules and ethical decision making.

Interdisciplinary aspects

Many links are possible with other disciplines, and although applications to terrestrial domains e.g. sociology, philosophy and military will be in-direct, benefits are still likely to result.

1.6.2. Key issue 15: What criteria shall be accepted for the medical selection of astronaut crews for human exploration missions?

This is a current and on-going issue for space medicine. Future medical selection will be coherent with state of the art knowledge, capabilities and accepted ethical practices. Astronaut medical selection is under continuous evolution, but remains in-line with the progress of medicine.

The following recommendations are made:

- Maintain the best practice for minimal individual risk exposure.
- If genetic screening or other screening methods are proven to reduce risk, these methods should be considered for use.

Interdisciplinary aspects

Many links are possible with other disciplines and although applications to terrestrial domains e.g. sociology, philosophy and military will be in-direct, benefits are still likely to result.

1.6.3. Key issue 16: What psychological criteria shall be used for the medical selection of astronaut crews for human exploration missions?

This is a current and on-going issue for space medicine in that society and personal behaviour norms evolve over time. All aspects of psychological selection will be coherent with state of the art knowledge, experiences and accepted ethical practices. Astronaut psychological selection is continually under evaluation in line with terrestrial psychology and psychiatry progress.

The following recommendation is made:

- If psychological screening methods are proven to reduce mission risks and optimise team dynamics whilst also increasing the likelihood of selecting appropriate crew for exploration missions, then these methods should be evaluated and considered for use.

Interdisciplinary aspects

There are clear links with other social and psychological / psychiatric disciplines in relation to space and terrestrial healthcare for similar circumstances involving small group dynamics and stressful activities.

2 Medication in Space

2.1. Introduction

Whenever drug treatment is needed, medication must be effective. Drugs may be used during spaceflight for several purposes, including:

- Emergency situations
- Acute intervention (emergency drugs, possibly including stored blood products)
- General medical issues (e.g. pain, infection, sleep problems, gastrointestinal problems)
- Pharmacological countermeasures during transition phases to support the cardiovascular and/or vestibular systems during launch and landing, or to ameliorate the effects of long-term stays in space (bone, muscle, radiation, cardiovascular system, sleep, immune system, kidney, vitamin supplementation etc.)

The 'Medication in Space' Expert Group based its work on the evaluation of issues it identified as relevant for its area of expertise. Of these issues and considering the inputs received from the community, the Group came up with a list of 9 Key Issues of the highest priority grouped in four overarching themes:

- Importance of effective drug treatment in human spaceflight
- Unwanted side effects and toxicity of medication in space
- Effects of spaceflight on pharmacokinetics
- Effects of spaceflight on pharmaco-dynamics

The priorities of research necessary to support foreseen space travel and planetary exploration represent a unique set of problems whose solutions demands an in-depth understanding of the whole human body and cross-disciplinary work between life scientists, engineers and technologists. All the necessary expertise has been acquired by European scientists during the past decades. In the context of the THESEUS project, the objective of this Expert Group was to gather this European expertise and create synergies, allowing an integrated approach on emerged priorities of research. Because of the necessary holistic approach, those research programmes obviously required the involvement of scientists whose expertise is disseminated across Europe.

The following sections present the conclusions the 'Medication in Space' Expert Group. This group met during two expert workshops in 2010. The workshops were organised sessions aimed at considering the key questions to address, the latest developments, the gaps to fill and the Earth-based applications.

The Expert Group recommends that key issues presented in this report are considered at their true value and addressed in future research programmes.

2.2. Importance of Effective Drug Treatment in Human Spaceflight– Key Issues

2.2.1. Key Issue 1: Is there evidence supporting changes in drug efficacy in-flight?

The fact that a gap in knowledge currently exists on this topic caused the expert group to consider this of highest priority given the unacceptable risks that would result during an exploration mission should space-induced drug changes be evidenced in-flight. There is some evidence of changes in pharmaco-dynamics and kinetics and reports of altered molecular mechanisms due to space flight. Unfortunately, too few in-flight or ground simulation studies have been conducted for adequate insight in to the matter. The expert group recommends implementation of a structured programme to increase knowledge of drug efficiency in space, and thus, ensure proper treatment of astronauts in-flight.

Interdisciplinary aspects

There is a clear link with radiation and immunology issues. Progress in the field of space pharmacology is of concern to the terrestrial pharmacology domain as increased knowledge concerning space induced pharmaco-dynamic and kinetic changes in relation to microgravity will have a bearing on pharmaceutical use in the 1-G supine, seated and upright positions and will thus be of clinical interest.

2.2.2. Key Issue 2: Which systems/pathways are operationally important for human spaceflight and why?

Studies with micro-arrays have demonstrated that many systems (e.g. adrenergic system, immune reactivity pathways and metabolism) change with altered gravity.

There is a knowledge gap concerning human drug receptor systems and pathways under spaceflight conditions. Any improvement in related knowledge will be relevant to human exploration missions and will aid the understanding of and improve the ability to master mission related risks. At the present time, few studies have been conducted in relation to this issue. Future studies should focus on the systems of high importance for drug efficiency in space that are most likely influenced by microgravity.

Interdisciplinary aspects

Clear links exist between Earth and space medicine issues and a better knowledge of drug receptor systems and pathways, in particular linked with the environment, will be of benefit to both terrestrial and space medicine.

2.3. Unwanted Side Effects and Toxicity of Medication in Space – Key Issues

2.3.1. Key issue 3: What classes of drugs should be studied as a priority to sustain the health and performance of astronauts during spaceflight?

The following classes were highlighted:

- Alpha-mimetics (orthostatic intolerance)
- Analgesics (back pain)
- Antiemetics (Space Adaptation Syndrome)
- Catecholamines (emergency medicine)
- Sleeping pills
- Antibiotics (bacterial Infection)
- Anti-mycotics (fungal infections)
- Medication against bone changes (bisphosphonates etc.)
- Medication for Radiation Protection (e.g. solar particle events)
- Nutraceuticals (specific nutrition based medication)

The fact that a gap in knowledge currently exists concerning the side effects and toxicity of medications (some already used in space) has caused the experts to view this issues as a highest priority given the unacceptable risks that would result during an exploration mission should this issue not be resolved. Unfortunately, too few in-flight and ground simulation studies have been conducted to date for adequate knowledge on the matter.

Several classes of drugs should be prioritised for study in order to properly sustain the health and performance of astronauts during spaceflight. Future work and suggested solutions should take into account the possible frequency of use of various drugs by astronauts in space, which drugs are commonly used, during what situations (extant and expected), preventative use and possible impacts on performance in addition to possible unwanted side-effects. Drug tests should also involve terrestrial analogues such as bed rest, animal models, cellular and molecular studies as well as in-flight studies with astronauts as subjects.

Interdisciplinary aspects

Clear links exist with many medical and physiological issues. Improvements in the knowledge of the side effects and toxicity of medication in the space context is of concern to the terrestrial pharmacology domain in so far as it increases the knowledge of drug use in relation to human physiology and the effects of the environment on this relationship.

Figure 7: ISS Medication Kits (Credit: NASA)

2.3.2. Key issue 4: Which drugs may have what important unwanted effects? What classes of drugs should be studied to prevent toxicity and risk issues during human spaceflight? What are the important drug interactions that should be avoided?

Each drug from the list above may have important unwanted effects, however, very little is known concerning additional, space-specific side effects and/or interactions. This gap in knowledge is relevant to human space exploration, but unfortunately, no studies have been conducted in-flight or during microgravity ground simulations. The development and use of a database on drug side effects and interactions is recommended as a precursor to operational use of drugs during space exploration missions. Consequently, it will be necessary to establish a pharmacovigilance system on the adverse effects of drugs and of drug interactions used in space.

Interdisciplinary aspects

Clear links exist with medical and physiological issues. Improvements in the knowledge of the side effects and toxicity of medication in use in space will be of benefit to terrestrial pharmacology through an increased understanding of the generic pharmacodynamics and kinetics of drug use.

2.3.3. Key issue 5: What pre-flight or in-flight tests should be conducted to avoid or assess possible side effects such as allergic reactions, problems from pharmaco-genetics or influences on performance?

To avoid additional risks, the expert group recommends that genetic screening for possible hereditary alterations in drug effectiveness should be conducted for the selection of crew for human exploration missions. The expert group is aware of only one study conducted during microgravity ground simulations (head down tilt bed-rest). Genetic screening for possible hereditary alterations in drug effectiveness should be implemented during the basic medical assessment of astronauts, as it may save them from future negative side–effects of drug use.

Interdisciplinary aspects

This is essentially a terrestrial medical matter. However, a clear link with space medicine exists in relation to the selection of astronauts. In this regard terrestrial progress can be applied for space medicine benefit.

2.3.4. Key issue 6: What tests should be conducted to assess the possible influences of medication on pre-flight and in-flight performance and sleep quality?

Some examples of standard tests that should be conducted include; neuro-physiological measurements (including EEG, EMG and EOG) and psychomotor tests including cognitive batteries. To avoid additional risk, the expert recommendation is that the influences of medication on astronaut in-flight performance should be conducted before human space missions begin. At the present time only anti-emetic medication is tested before flight due to their systematic use pre- and in-flight. As there are currently no standard tests for other medication use in the spaceflight, aviation or driving domains, appropriate assessments should be developed as a high priority. These tests should first be applied on earth and subsequently in flight when they are established.

Interdisciplinary aspects

Effective sleep and high performance are crucial for the safety of astronauts and other humans working in fields where a high level of vigilance is required. Consequently clear links exist with the aero-space, military and driving domains. Terrestrial progress in this regard will be of benefit when applied to space medicine.

2.4. Effects of Spaceflight on Pharmacokinetics– Key Issue

2.4.1. Key issue 7: It is important to know whether the pharmacokinetics of various drugs in space is altered. What pharmacokinetic changes in what classes of drugs have the most important clinical impact in space?

The spaceflight environment induces physiological changes which may influence drug pharmacokinetics at different levels. These physiological effects may modify the pharmacokinetics of the drugs administered in-flight producing a modified disposition leading to reduced pharmacological activity or the appearance of adverse side-effects. Data from bed rest studies have demonstrated changes in pharmacokinetics of certain drugs used as probes, e.g., lidocaïne (hepatic blood flow), oral acetaminophen or promethazine (digestive absorption).

It is important to know whether the pharmacokinetics of various drugs in space is altered. Research is required on the spaceflight-induced pharmacokinetic changes of different classes of drugs and on the identification of those likely to have the most important clinical impact during manned space.

This needs to be addressed especially for drugs that are expected to be used in-flight. Drugs with a narrow therapeutic window will require more attention. Investigations should be achieved in relation to the environment, under micro- and hyper gravity conditions as well as with respect to sedentary lifestyle and subject position (upright, seated, supine/bed rest, head-down tilt).

Tests should also be done in flight with sub-clinical doses to assess changes in the kinetics of the respective drug. They should also include different routes of administration to find out the best method of use in space.

2.5. Effects of Spaceflight on Pharmaco-Dynamics – Key Issues

Evidence from molecular research has demonstrated that expression and function of some receptors and signal transduction mechanisms in several cell types, may be changed in microgravity (e.g. adrenergic receptor sensitivity, lymphocyte second messenger systems). Therefore the effectiveness, i.e., the pharmacodynamic characteristics, of several classes of drugs are likely to be altered in space, however, no detailed studies have addressed this topic yet.

Human studies shall have top priority. A data base should be established to document the clinical effectiveness and side effects of drugs used in space and to compare these with terrestrial equivalents. To closely monitor drug effects, specific and standardised tests and questionnaires should be developed and used during human space flight operations. The tests and questionnaires must be short and simple to use to minimise in-flight crew time use.

Animal studies are also prioritised. Wild type and transgenic mouse models may be used to answer specific questions arising from observations in astronauts or molecular changes observed in cellular studies. These animal studies may be most appropriately performed using Biosatellites. Cellular/molecular studies shall also be considered a top priority.

Cellular/molecular studies are easy to be implemented and can deliver high quality information on changes in drug effects and signal transduction cascades as well as in pathogen physiology. Clinostats and centrifugation experiments will help to better characterise the effects of gravity on cells and to identify the most relevant questions that can be addressed by in-flight experiments. In the next few years the excellent Russian Biolab and ISS facilities should be extensively used in this respect.

2.5.1. Key issue 8: What evidence exists of pharmaco-dynamics changes resulting from posture and physical (in) activity seen in clinical studies (bed ridden patients, sedentary people)?

There is a knowledge gap concerning pharmaco-dynamics and subject posture and activity levels. Any improvement in knowledge will be relevant to human exploration missions and will aid the understanding of and improve the ability to master mission related risks. At the present time few studies have been conducted in relation to this issue

2.5.2. Key issue 9: What models should be used to study pharmaco-dynamics?

Appropriate models for the study of space induced changes in pharmaco-dynamics are; human studies i.e. bed rest (supine vs. upright, head down tilt), space flight and dry immersion; animal studies (tail suspension, hyper-gravity, space flight, wild type, transgenic/knock out), tissue/cellular/molecular studies such as Klinostat/random positioning, centrifugation, and in-flight experiments (e.g. biosatellites, ISS), as well as computer simulation models (in silico).

3 Annex: Expert Group Composition

Health Care - Cluster Coordinator:

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Götz Kluge	DLR - Institute of Aerospace Medicine, Germany
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Edition :
INDIGO
1 rue de Schaffhouse • 67000 Strasbourg
tél. : 06 20 09 91 07 • scop.indigo@gmail.com

ISBN : 979-10-91477-05-5
printed in E.U. march 2012

The THESEUS Coordination and Support Action has received funding from the European Community's 7th Framework Programme (FP7/2007-2013) under grant agreement n°242482.
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