



**THESEUS ROADMAP**



The University  
Of  
Sheffield.

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## **THESEUS: Towards Human Exploration of Space – a European Strategy**

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Previous space missions in low Earth orbit have demonstrated that human beings can survive and work in space for long durations. However, there are several pending technological, medical and psychological issues that must be resolved before adventuring into longer-duration space missions (e.g. protection against ionizing radiation, psychological issues, 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**

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The basis of this activity is the coordination of 14 disciplinary Expert Groups (EGs) composed of key European and international experts. 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**

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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 high priority disciplinary scientific topics or methodology issues representing challenges or opportunities 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.

In identifying Key Issues, the THESEUS Expert Groups considered the challenges imposed by the most demanding space exploration scenario proposed in the first steps of the THESEUS project, this led the groups to study knowledge gaps to be filled and methodological approach required **to implement a long duration mission to Mars (in the range of 500 days).**

The outcomes and main findings of the Expert Groups have been compiled into cluster reports and discussed during a synthesis workshop held in June 2011. From the reports and the discussion, DLR (under the coordination of Dr. Gerda Horneck and Prof. Rupert Gerzer), with support from the other THESEUS partners oversaw the integration and drafting of the THESEUS roadmap presented in this document



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## 1. Executive Summary

Future exploration of the solar system and beyond will undoubtedly be a collaborative endeavour of both humans and robots, enabled by innovation, ingenuity and global cooperation. Physical, psychological and technological challenges are inherent to human spaceflight, and become increasingly difficult to understand and overcome with longer-duration missions. Future exploration class missions may last up to several years, exposing astronauts to extreme environmental conditions and physical stressors that could cause major issues in both health and performance. Currently, some of these issues are showstoppers for human missions to e.g., Mars and need to be resolved. To truly enable and allow for future endeavours, the approach to space exploration-enabling research must be over-hauled.

Besides system-level investigations and studies, a complete understanding of the integrated response and adaptation to space and planetary surface environments as well as of interactions with the spacecraft and between crew members is necessary. Once multi-system responses to various stressors are understood, holistic countermeasures can be developed. Additionally, standardised protocols should be implemented to allow for cross-discipline comparison of data through available databases. To implement this essential integrated research approach, a stable, cross-disciplinary programme needs to be established at the European level.

THESEUS (**T**owards **H**uman **E**xploration of **S**pace: a **EU**ropean **S**trategy) is a Coordination Action funded by the European Commission seventh Framework Programme (FP7). This project aims to provide a cross-cutting, life science-based roadmap for Europe's strategy towards human exploration of space. To achieve its objectives, the project set up 14 Expert Groups (EGs) centred around five main research areas: integrated systems physiology, psychology and human-machine systems, space radiation, habitat management and health care.

With inputs from the wider scientific community, THESEUS experts identified 99 Key Issues, **Key Issues can be defined as high priority disciplinary scientific topics or methodology issues representing challenges or opportunities for human space exploration, requiring further attention in the future.** In identifying Key Issues, the THESEUS Expert Groups considered the challenges imposed by the most demanding space exploration scenario proposed in the first steps of the THESEUS project, this led the groups to study knowledge gaps to be filled and methodological approach required **to implement a long duration mission to Mars (in the range of 500 days).**

To enable research of the recognised key issues, the THESEUS roadmap has developed a three-themed approach with underlying recommendations:

### Theme 1: Develop an integrated view of human adaptation to the space environment

**Recommendation 1:** Perform a detailed, integrated survey, define and quantify the multiple environmental stressors during human space exploration missions, and assess their potential hazards to humans, both individually and in combinations.

**Recommendation 2:** Perform an integrated survey and identify interactive human adaptations to the complex environments of space exploration in order to assess the risks to astronauts and develop efficient countermeasures for their mitigation.

**Recommendation 3:** Perform an inventory of personalised exposures and responses to the complex environments of space exploration with regard to gender-based differences, genetic disposition and other individual characteristics.



**Recommendation 4:** Perform an integrated risk assessment for human exploration missions combining the risks from exposures to multiple-stressor environments, the interactive adaptations to these stressors, and from personalised responses. This should be the base for quantifying acceptable risks for astronauts during exploration missions.

### Theme 2: Develop an integrated view of countermeasures to multiple stressors

**Recommendation 5:** Mitigation strategies against certain adverse effects expected from environmental stressors should be implemented during the planning phase of a space exploration mission, e.g., by designing appropriate habitats, developing training methods and providing appropriate countermeasures with the mission scenarios and timelines.

**Recommendation 6:** Develop optimised countermeasure procedures and programmes that integrate human body functions as well as inter-individual variability, and take into account the possible interactions between different countermeasures. To achieve this, ground-based analogue facilities need to be developed for animal and human studies addressing system-level questions.

### Theme 3: Develop an integrated view of tools and methods

**Recommendation 7:** Develop standardised protocols and procedures for studies on integrative human adaptation to the conditions of space during exploration missions and the development of efficient countermeasures.

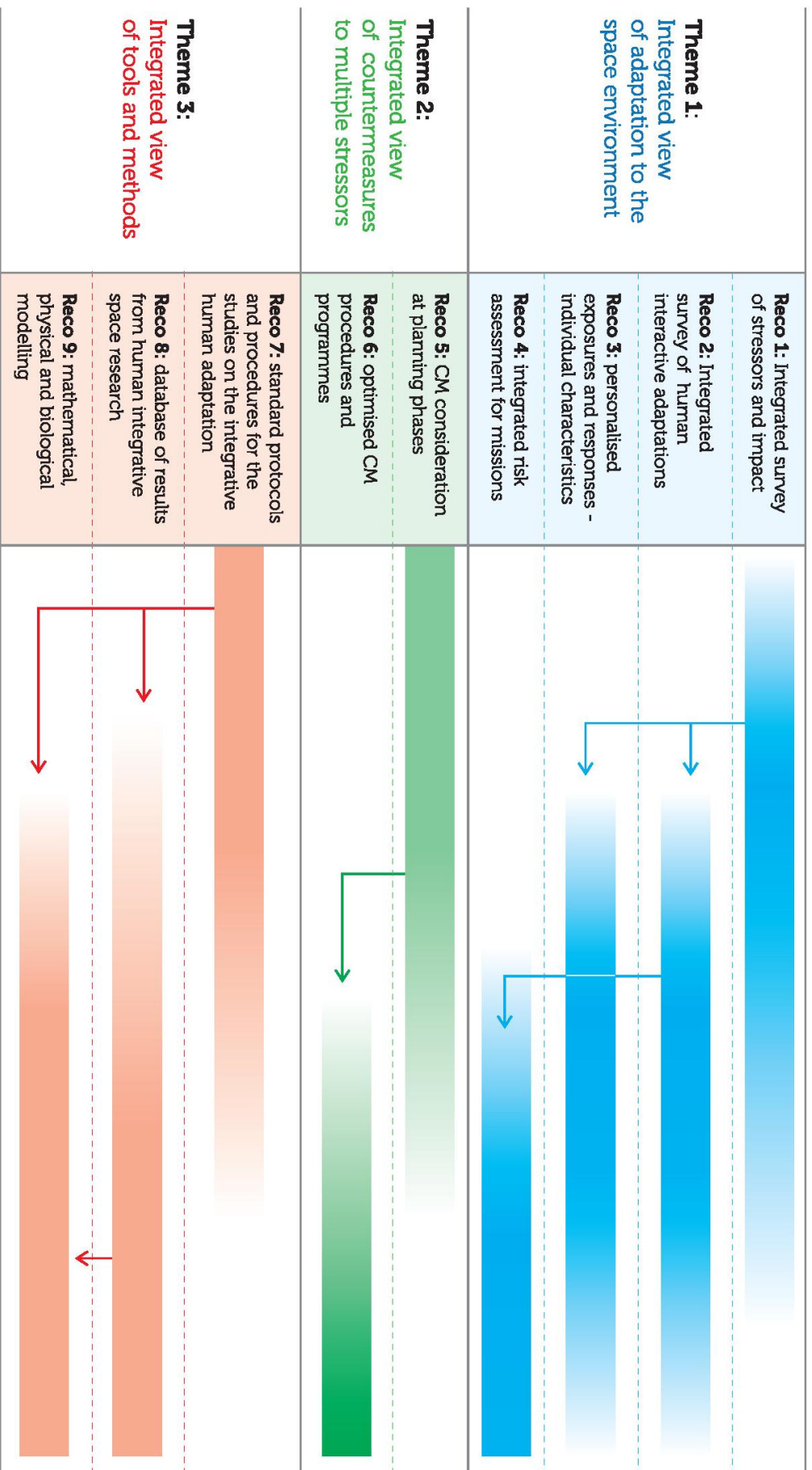
**Recommendation 8:** Set-up a database of results from ground and space-based integrative human research based on standardised protocols and procedures including the exertion of countermeasures. A data management and distribution system should be established in coordination with major European stakeholders (especially ESA and EC) to make these data accessible to the scientific community. Protocols should be established for disclosure of anonymous crew health data to qualified researchers.

**Recommendation 9:** Utilise mathematical, physical, biological and neurocognitive modelling to understand and anticipate various risks to astronauts associated with exploration missions and for applying means to reduce them to an acceptable level.

Overall, Europe is currently one of the world leaders in space technology and research. However, a long-term plan with research prioritisation enabling human spaceflight is lacking. The THESEUS roadmap proposes implementation of its recommendations in an integrated, phased approach. Such an approach complements fundamental research activities with programmes oriented around well-defined goals and objectives relevant to enabling future human exploration missions and ensuring European competitiveness in future exploration endeavours.

#### **Overarching Recommendation:**

**Structure human exploration-enabling research around the themes and recommendations put forward by THESEUS, using the phased approach defined by the roadmap exercise. Programmes should be coordinated and implemented at the European level and consider direct funding, networking and exchange of knowledge as well as optimised utilisation of European research infrastructures. In this context, targeted calls and dedicated research solicitation would allow medium to long-term consistency in the process.**



*THESEUS Roadmap – Articulation of research orientations in the future. The colour range indicates the phasing of a given recommendation – the darker the colour, the more intense activity*







### **From Space to Earth**

By and large, issues that humans face during space missions in LEO and beyond have commonalities with issues for individuals on Earth. Key Issues put forward by the THESEUS experts are fully relevant to societal challenges such as ageing, nutrition, civil security and individual safety as well as sustainable development.

It should be emphasised that while some topics are already intensively investigated on Earth, space exploration provides very specific conditions in terms of the environment, technical constraints as well as operational and safety requirements. These specificities allow consideration of scientific and technological topics with a different angle, bringing added value to many Earth applications. The issue of miniaturisation of diagnostics and health monitoring equipment provides a good example of such added value.

## **2. The Role of Europe in Global Space Exploration**

### **2.1. International context and background**

Space exploration requires global collaboration to succeed due to its extreme complexity and technological challenges. In May 2007, fourteen space-faring nations agreed on a coordinated approach to space exploration, the “Global Exploration Strategy” [1]. The European Space Agency (ESA) and space agencies from four European member states [ASI (Italy), BNSC (United Kingdom), CNES (France) and DLR (Germany)] agreed to take part in this initiative. This framework for coordination presents a vision for robotic and human space exploration, focusing on destinations within the solar system where humans may one day live and work. Robotic exploration will undoubtedly precede human exploration of the Moon, near-Earth asteroids and Mars to characterise the extra-terrestrial environments, assess risks connected to human missions and identify potential resources to be used for life support and technology purposes. Therefore, space exploration-enabling research must be geared towards both robotic technologies and human factors.

In 2007 the European Science Foundation (ESF), under the guidance of its European Space Sciences Committee, was commissioned by ESA to develop a science-driven scenario for space exploration. The resulting scenario [2-3] acknowledged that the drivers for human exploratory missions include science, technology, culture, and economic aspects. Above all, the search for habitability and, hence, for life beyond Earth, has been considered as one of the main intellectual driving forces in the endeavour to explore the Solar System, and the scenario emphasised that exploration without humans lacks an important societal and even scientific interest. Therefore, it was recommended that human spaceflight be integrated into the European Exploration Programme in a synergistic way at all stages of programme development and that the programme focuses on targets that can ultimately be reached by humans.

During the same year and based on inputs received by various stakeholders (including ESF), ESA developed a European long-term strategy for space exploration [4] focused on four key themes with particular significance for Europe:

- *The advancement of scientific knowledge: Life and its co-evolution with the planetary environment (main objective as per ESF’s 2007 science-driven scenario); lunar observatories; life sciences.*
- *Innovation and economic development: Applied microgravity research; entrepreneurial activities; space services.*
- *Support for the European political project: European ambitions; the Lisbon strategy; global partnership.*
- *Public constituencies, which recognise the necessity to engage the general public.*



This strategy foresees prolonged human operations in space, particularly in low Earth orbit through utilisation of the ISS. Through these activities knowledge will be gained on how to sustain human health in space and ways to improve the efficiency and safety of human transport and operations in space will be discovered.

Europe has the benefit of being able to rely on the heritage of its past space activities in various scientific and technological areas, making them a desirable partner in the global space exploration scenario. Noting that Europe has committed to participate in international space exploration initiatives, the Space Advisory Group (SAG) of the European Commission recommended that Europe should prepare a European vision for space exploration and invest its key competences in these international efforts [5], [6].

The need for a European Space Exploration Programme is rooted in the European space policy, e.g., in Article 189 of the TFEU (Treaty of the Functioning of the European Union), which calls for the EU *"to support research and technological development and coordinate the efforts needed for the exploration and exploitation of space."* This was further emphasised in the Council Resolution of 29 May, 2009, which *"reaffirms the need to assess the possibilities offered by European Union policies to embed space exploration in a wider political perspective and, recognising that space exploration has the potential to provide a major impact on innovation, looks forward to the Commission's proposed High-Level Political Conference on Space Exploration, on the basis previously agreed in the Space Council, as a first step towards the elaboration in due time of a fully-fledged political vision on "Europe and Exploration" encompassing a long-term strategy/roadmap and an international cooperation scheme"*. Following this resolution, the Second International Conference on Space Exploration in October, 2010, organised under the Belgian Presidency of the EU, concluded that *"space exploration satisfies the desire of humankind to discover new horizons. It is not only a scientific but also a political and global endeavour. Space exploration is a driver for innovation, technological development, and scientific knowledge which can bring about tangible benefits for citizens. It requires a long-term strategic vision for tomorrow's investments and embodies both cooperation and competition aspects"*.

A further step was made through the "Third International Conference on Exploration and the First High-level International Space Exploration Platform" held in Lucca (Italy) in November 2011. Highlighting that no single country can afford to explore the Solar System in a sustainable way alone, government representatives from 28 countries (21 of which were European partners) committed to begin an open structured, high-level policy dialogue on space exploration at the government-level [7].

## **2.2. Studies on future human exploration of space**

Several studies have been performed regarding research for enabling human exploration of the solar system. Notable initiatives include the Global Exploration Roadmap by the International Space Exploration Coordination Group (ISECG), ESA's HUMEX study, NASA's Bioastronautics Roadmap (later transformed into the Human Research Roadmap) and the US Space Studies Board's Decadal Survey on Biological and Physical Sciences in Space. Even though each study identifies key research areas that must be followed to enable human exploration, THESEUS takes a more holistic approach by providing a cross-disciplinary, multi-factorial approach to research and countermeasures.

Space exploration has several facets, including, for example, the scientific drive to acquire new insights into the emergence of life and the development of the Solar System. It requires a mix of robotic and human-related activities and promotes innovative technological and system development. The latest planning exercise was performed by the International Space Exploration Coordination Group (ISECG – established under the auspice of the GES). In its Global Exploration Roadmap [8] endorsed by 12 space agencies, ISECG defines a long-range human exploration strategy

that begins with the ISS and then expands human presence throughout the solar system, ultimately leading to human missions to the surface of Mars (Fig. 1). Under human exploration preparatory activities, the roadmap defines technology areas that need to be further developed, such as “*human health, life support and habitation systems, improvements in reliability, maintainability, reduced mass and volume, advancements in biomedical countermeasures, and self-sufficiency with minimal logistics needs as essential for long-duration spaceflight missions. In addition, advancements in space radiation research are required, including advanced detection and shielding technologies*”.

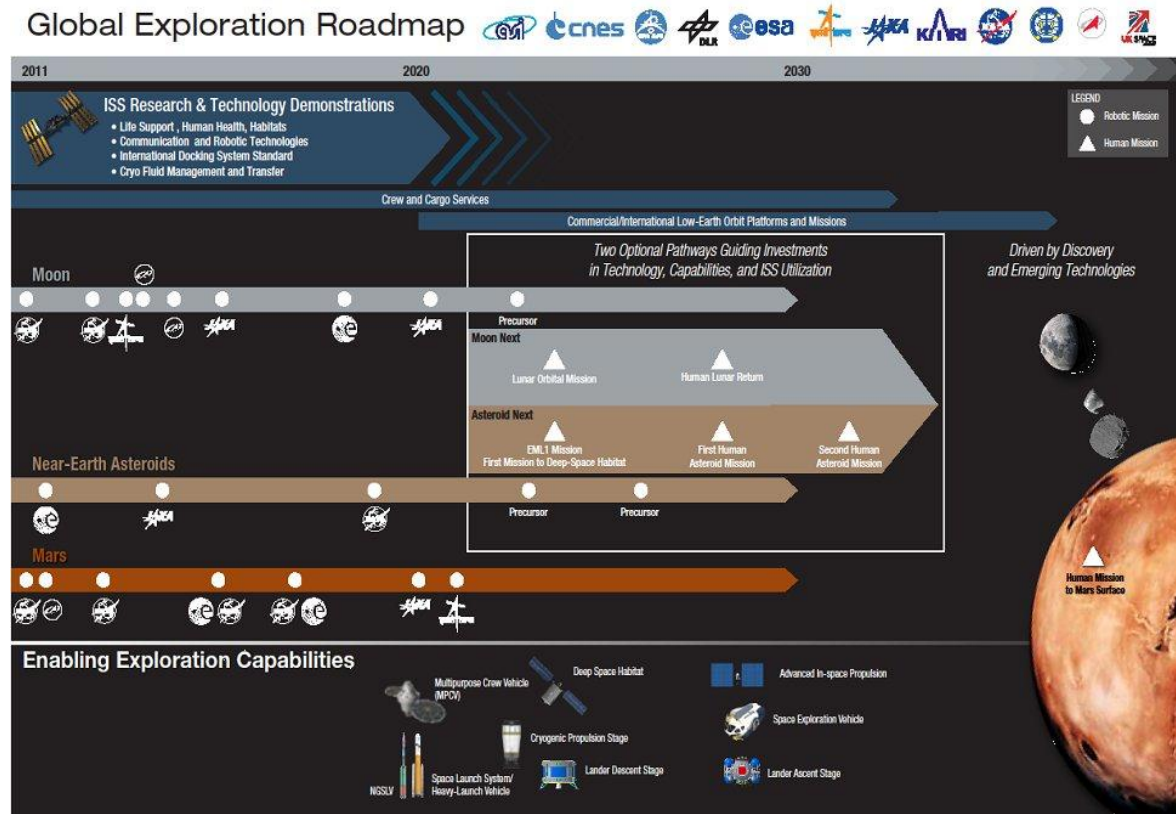


Figure 1. The Global Exploration Roadmap of ISECG (ISECG, 2011).

The Global Exploration Roadmap of ISECG mainly concentrates on flight scenarios and technology developments through the coordination of ISECG members.

In April 2011, ESA developed five major scenarios for future human spaceflight and exploration [9]:

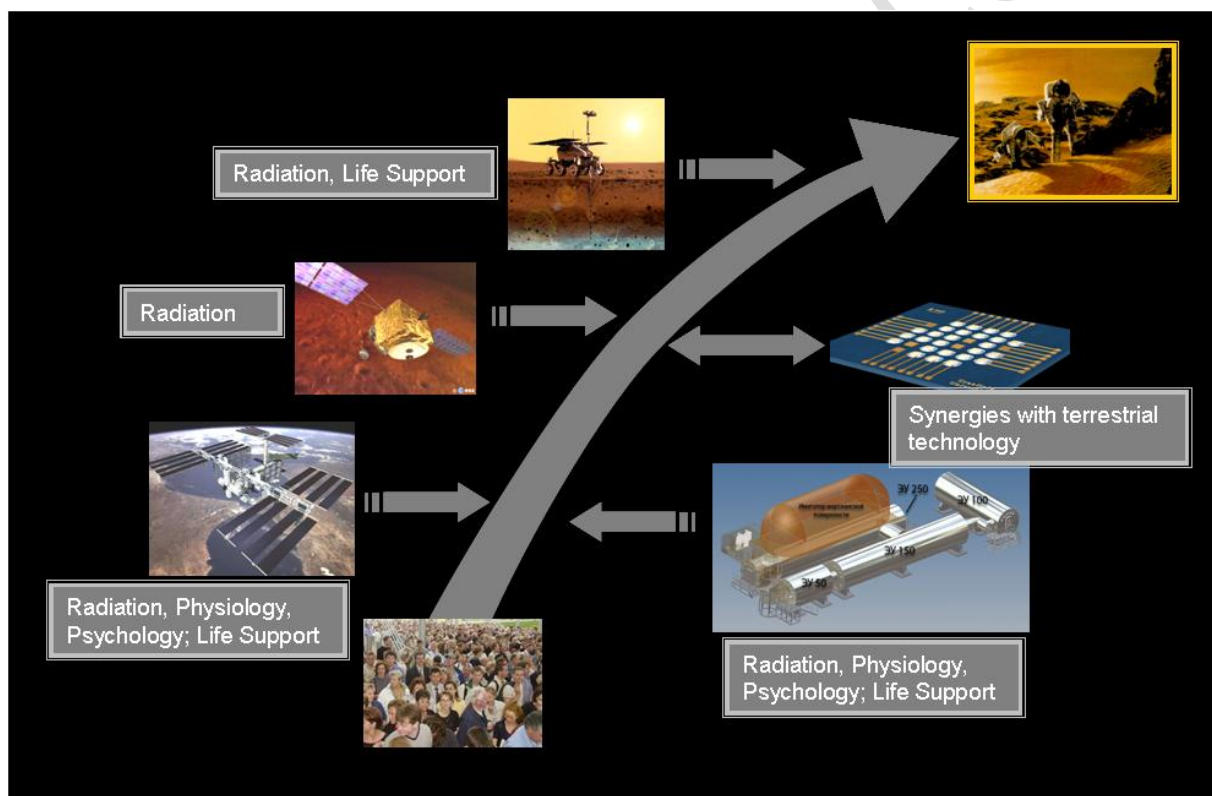
- *ISS, robotic precursor missions and technologies,*
- *Lunar exploration,*
- *Deep space operation,*
- *Autonomous capabilities for human transportation and operation in Low Earth Orbit,*
- *Multiple destinations to enable participation in multiple international mission scenarios.*

For each scenario, strategic guidance is outlined in view of ensuring sustained European access to man-tended infrastructures in space, and developing capabilities to enable and support human missions and operations in space. In addition, the study determines key activity lines, mainly dealing with critical technology to be developed. Roadmaps developed for the different scenarios of this study describe the potential missions to reach the goals. **The THESEUS study intends to contribute to this European strategy by providing a life sciences oriented roadmap required to safeguard humans during exploratory missions and to enable successful participation of Europe in the envisaged international human spaceflight and exploration scenarios.**

The first European roadmap for space exploration explicitly based on life sciences aspects was developed in the 2001 ESA study “HUMEX Study on the survivability and adaptation of humans to long-duration exploratory missions” (Fig. 2) [10-14]. The main recommendations of the HUMEX roadmap were:

- to largely use the ISS for research and development activities in the fields of space radiation health, psychology, physiology and life support systems;
- to make use of robotic precursor missions to explore planetary environments and their habitability, e.g., in view of radiation protection issues, hazards of planetary environments and in-situ resource utilisation for life support purposes;
- to use terrestrial test-beds and simulation facilities for understanding human and/or animal responses to simulated space parameters and to develop efficient countermeasures; and
- to develop synergies between space activities and terrestrial technologies and applications.

For the different flight and test scenarios, each field of research, including general health issues, radiation health, psychology, physiology, and life support systems, was considered separately. Relevant unresolved issues were identified, and needed research activities were suggested.



**Figure 2. The roadmap of the HUMEX study for a future European strategy in life sciences-related issues for human exploratory missions (adapted from ESA, 2003).**

In February, 2005, NASA issued the baseline document of its Bioastronautics Roadmap. This document was intended to list the major risks that crew may face during spaceflight and exploration missions. NASA’s Bioastronautics Roadmap was intended to guide prioritised research and technology development that, coupled with operational space medicine, inform: (1) the development of medical standards and policies; (2) the specification of requirements for the human system; and (3) the implementation of medical operations [15]. To this end, the roadmap describes and justifies a number of risks, with their context, severity rating, expected countermeasures and prioritised research and technology questions.



Following the development of knowledge and discoveries, this roadmap was regularly updated throughout its lifetime and eventually transformed into the Human Research Roadmap, the backbone of NASA's Human Research Programme (established in 2008). As of February 2012, NASA's Human Research Roadmap lists 31 risks clustered around 5 domains:

- Behavioural health and performance
- Exploration medical capability
- Human health countermeasures
- Space human factors and habitability
- Space radiation

The 31 identified risks are addressed through more than 600 research and technology development tasks [16]. Similar to the Bioastronautics roadmap, the Human Research Roadmap (and its associated programme) is continuously evolving and updated on a regular basis.

Another study dedicated to life science aspects of human spaceflight is the recently published "Decadal Survey on Biological and Physical Sciences in Space" of the US Space Studies Board's "Recapturing a Future for Space Exploration: Life and Physical Sciences Research for a New Era" [17-18]. This study was based on a request by NASA to achieve the goals of the Exploration Initiative: *A greater understanding of life and physical sciences phenomena in microgravity will be required as well as in the partial gravity environments of the Moon and Mars.* It is one of the goals of this study to recommend research that enables advancements in basic and applied knowledge needed to expand exploration capabilities. Topics that were considered for space exploration include:

- *Plant and microbial research to increase fundamental knowledge of the gravitational response and potentially advance goals for the development of bioregenerative life support;*
- *Behavioural research to mitigate the detrimental effects of the spaceflight environment on astronauts' functioning and health;*
- *Human and animal biology research to increase basic understanding of the effects of spaceflight on biological systems and to develop critically needed countermeasures to mitigate negative effects of spaceflight on astronauts' health, safety, and performance;*
- *Translational and applied research in physical sciences that can provide a foundation of knowledge for the development of systems and technologies enabling human and robotic exploration [17].*

The intent of this Decadal Survey is to lay out steps for developing a portfolio of research that is required for space exploration. Besides developments in technology the following actions were recommended:

- *Implement an effective countermeasures programme to attenuate the adverse effects of the space environment on health and performance capabilities of astronauts, a development that will make it possible to conduct prolonged human space exploration missions.*
- *Develop a deeper understanding of the mechanistic role of gravity in the regulation of biological systems (e.g., the mechanisms by which microgravity triggers the loss of bone or cardiovascular function – an understanding that will provide insights for strategies to optimise biological function during spaceflight as well as on Earth (e.g., slowing the loss of bone or cardiovascular function with aging) [18].*

This Decadal Survey represents the first study to explicitly mention cross-cutting issues for research related to humans in the space environment. It includes horizontal multi- and trans-disciplinary integration as well as a vertical interaction among basic, preclinical, and clinical scientists to translate fundamental findings into improvements in the health and well-being of crew members during and after their missions. It also recognises that an integrated research approach is warranted to address

the sum effect of a range of physiological and behavioural changes during long-term human spaceflight. This is similar to the integrated and holistic approach that THESEUS aims to implement on the European level.

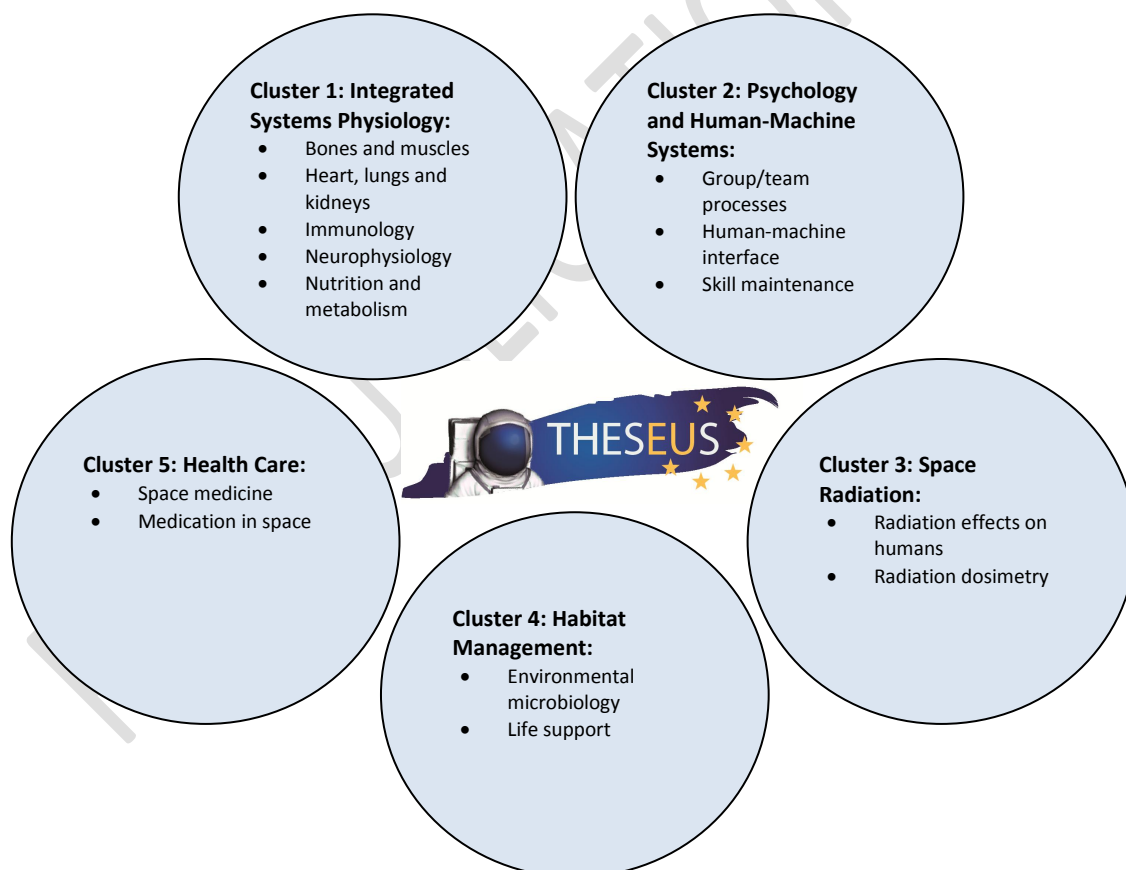
### 3. THESEUS Process and Approach

#### 3.1. Identification of Key Issues

*THESEUS aims to provide a life science-based roadmap for Europe's strategy towards human exploration of space.*

THESEUS was initiated in early 2008 with the ambitious objective to perform a wide survey of knowledge gaps that must be filled to enable further human space exploration, in particular beyond LEO, and to suggest research activities to address these gaps. As a horizon scanning initiative, the project cuts across all life science domains relevant to human space exploration ranging from integrated physiology to habitat management and health care. THESEUS also aims to identify how research for space exploration can also be relevant to health and societal issues on Earth.

To achieve its objectives, the project set up 14 disciplinary Expert Groups (EG) clustered around five areas of research:



Each EG involved about ten international experts, spanning from Europe, USA, Russia and Japan. Special attention was given to ensure involvement of members from ESA topical teams in life sciences, and that links with the NASA Human Research Program were made via participation of US investigators actively involved in this programme. Overall, the THESEUS Expert Groups involved 123 experts from 23 different countries.



The 14 EGs met in April, 2010 to brainstorm the current state of research in their specific field and identify the main research questions necessary to enable human space exploration. From these workshops, 112 Key Issues were identified by the EGs. **Key Issues can be defined as high priority disciplinary scientific topics or methodology issues representing challenges or opportunities for human space exploration, requiring further attention in the future.**

In identifying Key Issues, the THESEUS Expert Groups considered the challenges imposed by the most demanding space exploration scenario proposed in the first steps of the THESEUS project, this led the groups to study knowledge gaps to be filled and methodological approach required **to implement a long duration mission to Mars (in the range of 500 days).**

While the work performed by the EGs represents the core of THESEUS, the project also gathered inputs and comments from the wider scientific community on the identified Key Issues. This was made possible through a wide consultation consisting of 14 online questionnaires open to any interested scientist in the domains covered by the project. This community consultation was open for two months (between 15 July and 15 September, 2010), and contributions were received from 169 scientists (of which 149 were not members of any THESEUS EG). Considering the EG membership and community participation through the online consultation, a total of 272 investigators participated in elaborating the EG recommendations and eventually to the definition of this roadmap.

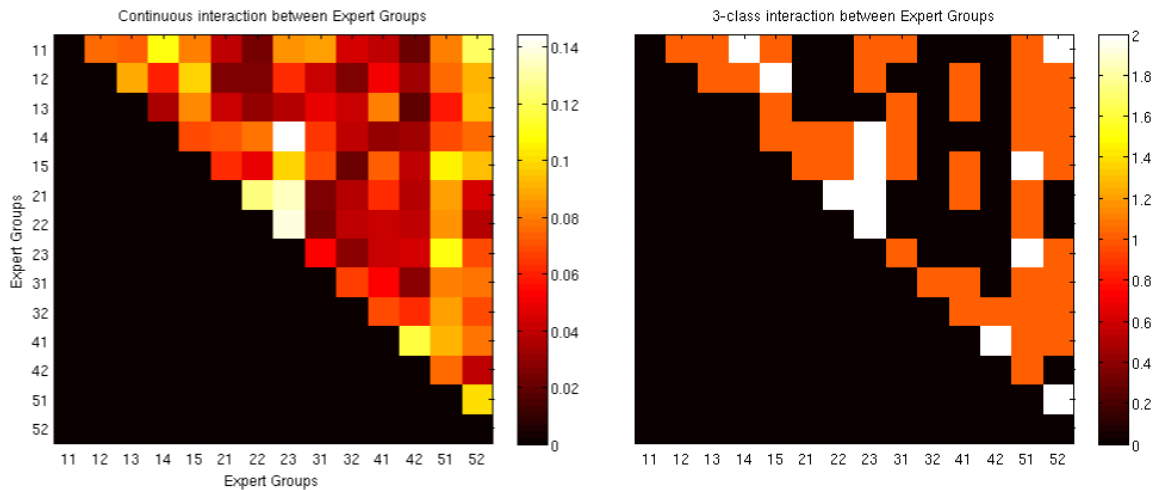
The third step of the THESEUS project focused on finalising the Key Issues and associated recommendations. To this end, EGs met in cluster in October, 2010 to review the inputs received from the community consultation, review the Key Issues in detail, and agree on the recommendations to be put forward. This step resulted in the final list of 99 THESEUS Key Issues (see Annex 1 for details), further detailed in the five cluster reports (published separately) [19-23].

It is important to remember that the THESEUS roadmap presented in this document is fully integrated with the work of the Expert Groups, and the cluster and Expert Group reports form the foundation upon which it has been built. The roadmap suggests a coherent way to address issues identified by the THESEUS experts and is strongly linked with the content of the cluster reports and therefore should not be considered independently from these.

### **3.2. Identifying areas of common interest**

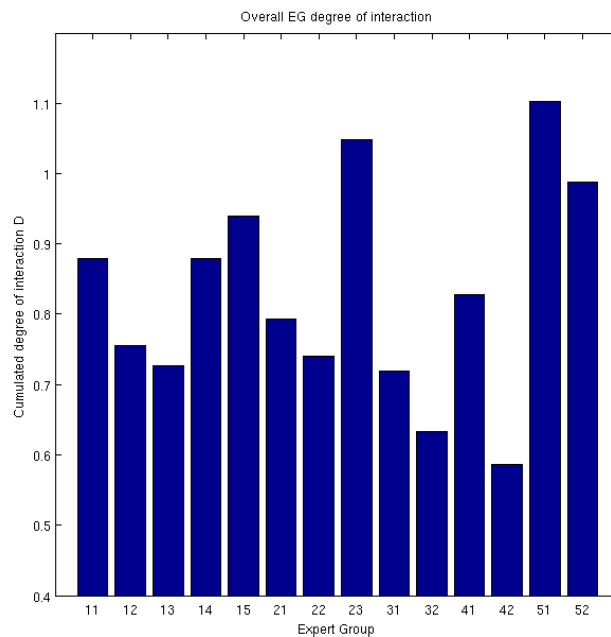
THESEUS considers human exploration-related research from a cross-cutting and integrated perspective. It is crucial that the findings and outputs from the EGs are considered in a holistic manner, interlinking Key Issues and identifying the best way to address them in a coherent and sensible way.

From the list of 99 Key Issues, identification of trans-disciplinary aspects was an essential step in THESEUS. Although experts dedicated special attention to identify elements at the boundary between different scientific domains, a more neutral, systematic analysis was conducted to confirm, visualise, and provide additional insights into overlaps. To evaluate the degree of interaction across the five clusters and their EGs, the following approach was adopted. First, specific keywords were extracted from individual EG reports. Next, metrics were defined to quantify the degree of interaction between Expert Groups. In short, the degree of interaction was proportional to the number of common keywords between the two reports. Normalisation of that parameter allowed for quantitative comparisons of trans-disciplinarity between EGs, resulting in the matrices presented in Figure 3.



**Figure 3. Continuous (left) and discretised interaction matrices (right), showing the degree of interaction between Expert Groups based on colour (lighter colour = more interaction, darker colour = less interaction). For the discretised matrix, 2 thresholds (degree=0.047 and 0.096) were adjusted to split the lognormal distribution of degrees of interaction (white = high, orange = medium, black = low degree of interaction) - EG numbering is provided in annex 1.**

Figure 3 (left) shows the continuous EG interaction matrix (the lighter the box, the more interactions). To enhance the contrast, two thresholds were defined based on the lognormal-like distribution of the degrees of interaction. Three classes resulted from this process: high (white), medium (orange) and low (black) degrees of interactions. Figure 3 (right) illustrates the discretised matrix of interaction. From these graphical representations, one can see that the EG focused on Dosimetry (32) and Life support (42) are the most independent EGs, whereas the EG focused on space medicine (51) interacts with every other EG. To quantify how much each EG overlapped with another EG, a cumulated degree of interaction was computed. This degree was defined as the sum of the interaction of that EG with every other EG (excluding itself). Figure 4 presents the cumulated degrees of interaction of each EG.



**Figure 4. Cumulated degree of interaction for each EG. - EG numbering is provided in annex 1.**





In addition to the ability to visualise interactions across elements in a matrix form, this method also allowed for the identification of concepts and issues that cut across the THESEUS scope, i.e., present an interest for a significant part of the THESEUS research domains. Six of the most transversal concepts are listed below by alphabetical order:

- **Contamination**

This mainly emerges from the Expert Group on habitat management and design, but contamination (microbial and Lunar/Martian material) is also of relevance for integrated physiology issues, including the cardiovascular system, immunology, nutritional issues, digestion, infections and sterilisation.

- **Individual factors**

Investigating the mechanisms behind why and how individuals respond differently to the conditions of spaceflight by various means (e.g., psychological assessments, genetic and medical screening) has been pointed out several times by THESEUS Expert Groups. This issue is relevant to develop a better understanding of human adaptation to spaceflight and could also be considered in the selection of astronauts and crew composition. While it is challenged by ethical issues, genetic predisposition seems to be a topic of increasing interest.

- **Molecular and cell biology; genetics**

This theme deals with every aspect of cellular and molecular mechanisms involved in various reactions to stressors at large. It is omnipresent: bones and muscles, genetics, immunology, contamination, radiation effects on cells etc. There was no explicit EG to deal with these mechanisms in THESEUS.

- **Monitoring and modelling**

Intelligent, integrated, synchronised monitoring of physiological and psychological systems together with the environment (e.g., radiation, habitat) are mandatory and will be extremely valuable to feed integrated models.

- **Integrated countermeasures**

Countermeasures must be approached in an interdisciplinary manner, firstly, because astronaut time is very constrained, and secondly because a comprehensive approach is much more efficient than the sum of local solutions. All dimensions need to be taken into account.

- **Radiation effects**

Negative radiation effects represent one of the most critical showstoppers for long-term spaceflight. Particles from mixed radiation sources are abundant in space, and conventional shielding by thickening the habitat is extremely challenging. Active shielding, forecasting events, and determining acceptable doses are all important aspects in protecting a crew from danger. Also, understanding the interaction of radiation with physiological systems is critical. Monitoring these events is of prime importance as well to feed prediction models.

#### **4. THESEUS Roadmap: Providing Relevant Orientations for Research**

THESEUS EG chairs and rapporteurs met for an integration workshop in June 2011 where individual EG reports and Key Issues were presented and discussed. Brainstorming sessions on how to structure the THESEUS roadmap and properly address EG Key Issues were held in plenary and splinter groups. During these sessions, three overarching, trans-disciplinary research orientations were identified:



**Theme 1: Develop an integrated view of human adaptation to the space environment**

**Theme 2: Develop an integrated view of countermeasures to multiple stressors**

**Theme 3: Develop an integrated view of tools and methods**

The transition from research on independent functions with regard to human responses to the space environment to a more integrated approach requires a focused, competitive research strategy for solving targeted risk areas of human health and performance during space missions. Reaching these goals will not only provide the basis for critical, high quality health care for crews on-orbit, but it will also result in a wealth of physiological, psychological and performance data to evaluate. Examination of these data will undoubtedly yield solutions to medical challenges associated with long-term spaceflights. The data will also provide the basis for well-conceived and evidence-based solutions to such physiological concerns as radiation exposure, immunology, mineral metabolism, protein synthesis, chronobiology, cardiology, and food and nutrition in space as a whole, and also the development of a new generation of countermeasures for both micro and low gravity.

The THESEUS roadmap is structured around these themes and connects each theme to the output and findings of individual EGs.

#### **4.1. Theme 1. Integrated view of human adaptation to the space environment**

Space exploration exposes astronauts to a number of inevitable stresses. In response, the human body reacts with a variety of symptoms, both physical and mental. Countermeasures need to be developed to mitigate the harmful, long-term effects of these stressors on astronauts for exploration mission to even be feasible.

To sustain astronauts' health, well-being and competence during exploration missions and after return to Earth, an integrative research programme is necessary. This will require an integrated survey and definition of the multiple stressors associated with human space exploration environments and identification of interactive adaptations to these complex environments [24]. Additionally, space exploration deals with a small number of members of a group, and therefore, a generalisation of human responses would not meet the requirements of individual astronauts. This fact requires, in addition to the integrative research work, a personalised view of individual responses. These three interconnected research circles of space exploration are shown in Figure 5, namely

- the complex interplay of environmental stressors,
- integrated human responses, and
- astronauts' individual response.

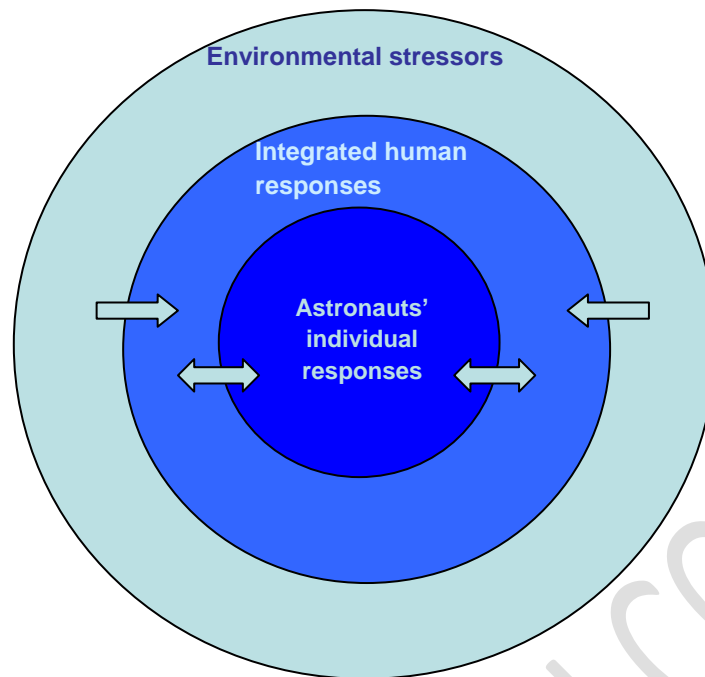


Figure 5. The 3 research circles of the THESEUS roadmap (Jack in the box scenario)

During exploration missions, humans are confronted with a complex interplay of environmental parameters and stressors not encountered on Earth. Stressors may arise from various sources including:

- flight dynamics, such as acceleration, vibration and noise during launch and re-entry, as well as microgravity and changes in circadian rhythms during spaceflight;
- outer space as an inhabitable environment (space vacuum, the radiation field in space, extreme temperature fluctuations) requiring protection from its hazardous components to the best extent possible;
- inhabitable planetary environments (Moon or Mars) with low gravity, an atmosphere not supportive for life or totally absent, intense radiation, planetary dust, extreme temperatures, and different daily rhythms;
- living and working in a habitat with an artificial atmosphere, specific habitat micro-flora, specific gravity levels (either microgravity or low gravity) altered circadian rhythms, increased levels of ionising radiation and physical confinement;
- long-term confinement in a spacecraft or habitat causing problems connected with the isolation of a small community.

Table 1 lists the main stressors imposed by spaceflight and how these impact human body systems. General health is defined as optimal physical and health conditions allowing the astronaut to perform tasks nominally. Cells marked with a question mark are areas where interactions are not known, thus requiring further investigation.

		STRESSORS									
		High g during launch and entry	Microgravity	Hypo gravity (Moon, Asteroid, Mars)	Radiation	Microflora	outside environment (dust, atmosphere)	Chronobiological factors	Nutrition	Confinement	Remoteness
HUMAN SYSTEMS	Bones and muscles	+	+++	?	+	?	?	+	++	++	∅
	Heart, lung and kidney	++	+++	?	+	+	+++	+	++	++	∅
	Immune system	?	+++	?	++	+++	++	?	++	++	?
	Genetic system	∅	?	?	+++	?	?	?	?	?	?
	Neurosensory system	+	+++	?	++	?	?	++	?	?	?
	Behaviour	+	++	?	++	?	+	+++	++	+++	+++
	General Health	?	+++	?	++	++	+++	++	+++	++	+

**Table 1: Impact of spaceflight stressors on crew (+++ high; ++ medium; + low; ? not known; ∅ No impact)**

While Table 1 provides information on the impact of individual stressors on crew members, it is crucial to consider and understand that these parameters do not necessarily act in isolation, but rather, synergistic interactions may occur. As an example, an unresolved issue is the possible interaction of microgravity and radiation on different human physiological and genetic functions. Radiation and microgravity may also alter other environmental parameters, such as the habitat microflora.

**Recommendation 1: Perform a detailed, integrated survey, define and quantify the multiple environmental stressors during human space exploration missions, and assess their potential hazards to humans, both individually and in combinations.**

In the past, most studies on the effects of spaceflight on humans have concentrated on specific body systems, such as bone and muscle, cardiovascular, immune, neurovestibular, genetics, and behaviour. However, to provide high quality health care to astronauts during exploratory missions, which may last months or even years, an integrated approach is required. This transition of human research in space from the study of independent physiological, genetic and psychological functions to an integrated approach requires a new research strategy. Many impairments and adaptations to the spaceflight environment and planetary habitats pertain to several body functions and are likely to be interdependent. Therefore, such studies of human adaptations to the stresses occurring during exploratory missions require a holistic systems approach [24]. Only a complete set of data on various body systems to spaceflight will provide the basis for well-conceived and evidence-based decisions for appropriate countermeasures and solutions to medical challenges during long-term space exploration missions.

**Recommendation 2: Perform an integrated survey and identify interactive human adaptations to the complex environments of space exploration in order to assess the risks to astronauts and develop efficient countermeasures for their mitigation.**



In addition to this integrative research approach for identifying interactive responses of the whole human system, a personalised view of individual responses of astronauts is advisable. There will be only a small number of astronauts selected for such long-term exploratory missions, and therefore, their individual responses to various stressors need to be evaluated. This also includes determining individual radiation exposure for each astronaut during each period of the mission. Another item to be considered is the possible hormonal-based gender differences in the response to spaceflight, which affect regulation of the central nervous system, bone metabolism or other body functions. Age and gender based differences can also be seen in radiation sensitivity. In addition, the possible role of genetic disposition to radiation and other spaceflight stressors needs to be elucidated.

***Recommendation 3: Perform an inventory of personalised exposures and responses to the complex environments of space exploration with regard to gender based differences, genetic disposition and other individual characteristics.***

A reliable assessment of human risks during exploration missions requires an understanding of the interaction and complex interplay between environmental stressors, the integrated human body responses and the astronaut's individual response. As an example, radiation risk assessments are available for Low Earth Orbit (LEO) missions [25-26]. The guidelines for radiation protection in LEO missions were derived from a postulated 'acceptable' risk for late cancer mortality, which was then justified through a comparison with mortality rates from 'normal' terrestrial occupations. Radiation exposures during previous spaceflight activities within the geomagnetic shield, in LEO and inside the ISS were sufficiently low and no special actions were necessary to keep within the NCRP limits. However, the expected doses during inter-planetary exploratory missions are likely to infringe these limits unless mass shields are installed, which could strain the capacities of the propulsion system, or active (electromagnetic) shielding is shown to be feasible and consequently -developed. In addition to late cancer mortality, and this is a decisive difference, the possibility that crew members might suffer from early radiation sickness induced by significant solar particle event irradiation – e.g. during extra-vehicular or extra-habitat activities implies a non-negligible risk for the astronauts [10]. Little work has been done to assess the risks to astronauts from the other inevitably present spaceflight stressors. Here, an integrated approach is necessary.

***Recommendation 4: Perform an integrated risk assessment for human exploration missions combining the risks from exposures to multiple stressor environments, the interactive adaptations to these stressors, and from personalised responses. This should be the base for quantifying acceptable risks for astronauts during exploration missions.***

#### **4.2. Theme 2: Integrated view of countermeasures to multiple stressors**

To safeguard astronauts' health, well-being and working efficiency, a comprehensive strategy to mitigate various risks is required. On one hand, this concerns qualitative and quantitative strategies to mitigate environmental stressors such as radiation, toxic substances in the habitat atmosphere, the rise of microbiological pathogens, microgravity-induced hypokinesia, and confinement and remoteness during the mission. On the other hand, countermeasures need to be developed to mitigate adverse responses to multiple stressors. Table 2 presents different types of countermeasures and their efficiency in compensating the stressors' effects.

		STRESSORS									
		High g during launch and entry	Microgravity	Hypo gravity (Moon, Asteroid, Mars)	Radiation	Microflora	outside environment (vacuum, dust, atmosphere)	chronobiology	Nutrition	Confinement	Remoteness
COUNTERMEASURES	psychological and skill maintenance countermeasures	+	+	+	∅	∅	∅	+	+	++	++
	Shielding	∅	∅	∅	+++	∅	∅	∅	∅	+	+
	Medication	+	+	+	+	++	+	++	+	+	+
	exercise countermeasures	+	+++	++	∅	?	+	+	+	+	+
	Nutrition	+	++	++	+	+	∅	+	+++	+	+
	Habitat design and safety	+	++	++	+++	+++	++	+++	+	+++	+++
	Mission Planning	+	++	+++	+++	+	+	+++	+	++	+++

**Table 2. Countermeasures effects to mitigate the effects of stressors (+++ high; ++ medium; + low; ? not known; ∅ No effect)**

Several adverse effects from environmental stressors during space flight can be mitigated through the design of an appropriate habitat, e.g., by providing means of radiation shielding, developing suitable monitoring and controlling systems for atmospheric pollutants and microbiological pathogens, constructing health-optimised countermeasure systems and providing a human-friendly living area with private areas for each astronaut. Additional mitigation can be achieved by planning appropriate mission scenarios and timelines, e.g., in order to reduce the chances of exposure to solar particle events. This would be one way to implement the best workable practices to assure that the crew is exposed to a radiation risk that is As Low As Reasonably Achievable (following the ALARA principle).

**Recommendation 5: Mitigation strategies against certain adverse effects expected from environmental stressors should be implemented during the planning phase of a space exploration mission, e.g., by designing appropriate habitats, developing training methods and providing appropriate countermeasures with the mission scenarios and timelines.**

Current exercise countermeasures are mainly targeted towards mitigating harmful responses of one specific system of the human body, such as bone and muscle degradation or orthostatic intolerance. For exploration class missions, a new approach is required that considers the benefits of physical and pharmacological countermeasures to the whole human body. In fact, countermeasures targeting one stressful response may actually be harmful or counterproductive for another one [27-28]. Suitable

animal and human facilities need to be developed for specially designed experiments that concisely pose and address system-level questions. One such Facility may be the newly developed :envihab Facility at DLR in Cologne.

		COUNTERMEASURES						
		psychological and skill maintenance countermeasures	Shielding	Health care including Medication	exercise countermeasures	Nutrition	Habitat design and safety	Mission planning
HUMAN SYSTEMS	Bones and muscles	∅	+	++	+++	++	?	+++
	Heart, lung and kidney	∅	+	++	+++	++	++	+++
	Immune system	?	++	++	+	++	+++	++
	Genetic system	?	+++	++	?	+	?	+++
	Neurosensory system	++	++	++	+	∅	+	++
	Behaviour	+++	++	++	++	++	+++	+++
	General Health	++	+++	+++	+++	+++	+++	+++

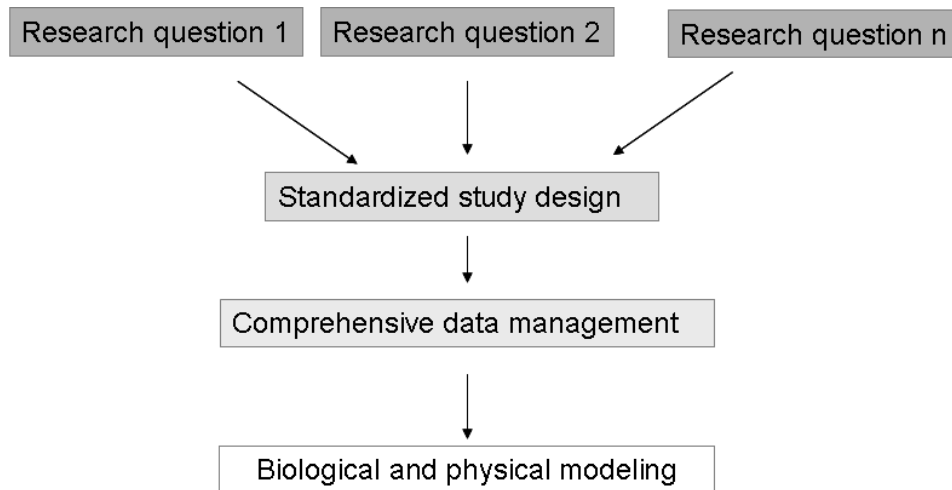
Table 3. Efficiency of countermeasure on human systems (+++ high, ++ medium, + low, ? not known, ∅ No effect)

**Recommendation 6:** Develop optimised countermeasure procedures and programmes that integrate human body functions as well as inter-individual variability, and take into account the possible interactions between different countermeasures. To achieve this, ground-based analogue facilities need to be developed for animal and human studies addressing system-level questions.

#### 4.3. Theme 3: Integrated view of tools and methods

An integrated research programme on human adaptation to the conditions of space and the development of efficient countermeasures (Themes 1 and 2) requires standardisation of the methods for experiment design, performance and analyses. Such a standardised approach would allow for different experiments in space and on the ground to collaborate, compare results and draw valid conclusions (Fig. 6). One example could include a series of bed-rest studies in which men and women are exposed to exactly the same conditions and countermeasures during the period of confinement.

**Recommendation 7:** Develop standardised protocols and procedures for studies on integrative human adaptation to the conditions of space during exploration missions and the development of efficient countermeasures.



**Figure 6. Scheme of an integrated approach to reach a comprehensive understanding of human responses to the conditions of space exploration and the development of efficient countermeasures (modified from [24]).**

In addition to standardising methods for experiment design, performance and analyses, the data collected by different teams of researchers should be made available to the scientific community in a comparable and usable form (including their context). Access should also be given to anonymous crew health data, retrospectively and prospectively. For this, protocols would have to be established for disclosure of operational performance data to qualified researchers. Maximum exploitation of currently available resources on Earth and in space, as well as respective databases is mandatory. Examination of these data will provide the basis for a critical, high quality health care for crews on orbit and will undoubtedly yield solutions for medical challenges for long-term spaceflights. To efficiently utilise all available resources, a comprehensive system of data storage and management must be set up. This shared database would provide the basis for well-conceived and evidence-based decisions to physiological concerns such as radiation exposure, immunology, mineral metabolism, protein synthesis, chronobiology, cardiology, and food and nutrition in space, taken as a whole as well as for the development of a new generation of integrated countermeasures.

**Recommendation 8: Set-up a database of results from ground and space-based integrative human research based on standardised protocols and procedures including the exertion of countermeasures. A data management and distribution system should be established in coordination with major European stakeholders (especially ESA and EC) to make these data accessible to the scientific community. Protocols should be established for disclosure of anonymous crew health data to qualified researchers.**

Modelling approaches are needed to simulate the complex environments encountered during exploratory missions, including the radiation field in space, gravity levels, the habitat design and their possible interactions. Biology-based modelling will add knowledge to a mechanistic understanding of the various risks and should be integrated in the design of the experiments. Mathematical modelling approaches are currently already being used for the determination of space radiation risk in the fields of physics. Biological modelling is also needed to understand the integrated responses of the human body to the complex field encountered. Studies are needed to transfer small scale molecular and cellular models into larger multi-scale models, representing the overall response of a tissue or the whole body. A model-based development of technologies is also mandatory for improving our understanding of the functioning of closed loops via multiple parameters, as needed for the development of human life-support systems. Dedicated multi-physics and multidisciplinary algorithms and software tools need to be applied, including models for thermo-fluid-dynamics,





biological processes, human metabolism and respiration, urine and faecal production, motor control, as well as for utilising and exploiting extra-terrestrial planet resources replenishment (ISRU).

***Recommendation 9: Utilise mathematical, physical, biological and neurocognitive modelling to understand and anticipate various risks to astronauts associated with exploration missions and for applying means to reduce them to an acceptable level.***

#### **4.4. Tying Key Issues to recommendations**

While the THESEUS roadmap addresses overarching research orientations and programmatic implementation, detailed Key Issues identified by the THESEUS experts represent the building blocks of this strategy. These Key Issues are numerous (99), and the THESEUS approach would allow each of them to be addressed in a comprehensive and rational manner. The relevance of recommendations to individual Key Issues are shown in tables 4 to 8.

Any of the nine structural recommendations have some particular relevance to address at least 1/3 of the Key Issues, and six of these recommendations are relevant to address more than half of the Key Issues.

**Table 4: Integrated Systems Physiology - Recommendation's relevance to Key Issues (+: significant relevance, ++: high relevance)**

			Theme 1. Integrated view of adaptation to the space environment				Theme 2: Integrated view of CM to multiple stressors		Theme 3: Integrated view of tools and methods		
			Reco 1: Integrated survey of stressors and impact	Reco 2: Integrated survey of human interactive adaptations	Reco 3: personalised exposures and responses - individual characteristics	Reco 4: integrated risk assessment for missions	Reco 5: CM consideration at planning phases	Reco 6: optimised CM procedures and programmes	Reco 7: standard protocols and procedures for the studies on the integrative human adaptation	Reco 8: database of results from human integrative space research	Reco 9: mathematical, physical, biological and neurocognitive modelling
<b>Bones and Muscles</b>	1.1.1	Sex-based differences in the preservation of musculoskeletal tissue during space flight	+	++	+	+	+	+	+	+	
	1.1.2	Effects of micro-gravity on musculoskeletal injuries and healing processes		++		++	+			++	
	1.1.3	Role of genetics in musculoskeletal performance, preposition to injury and overall adaptation to micro-gravity		++	+			++	+	++	+
	1.1.4	Biomechanics and impact of partial gravity on the musculoskeletal system		+		+	++	+			++
	1.1.5	Effects of radiation exposure experienced during space flight on the musculoskeletal system	++	++	+	++	++	+	+	+	++
	1.1.6	Ground-based human studies		++	+	+	++	+	+	++	++
	1.1.7	Ground-based animal studies		+	++	+	+	++	+	++	
	1.1.8	Optimise countermeasure efficiency and utilise an integrated physiology approach s		+			++	++	+		++
<b>Heart, Lungs and Kidneys</b>	1.2.1	What are the inflight alterations in cardiac structure and function?		++	+	++	+	+	+	+	+
	1.2.2	What is the influence of spaceflight on structure and function of blood vessels?		++		++	+	+	+		
	1.2.3	What level of cardiovascular function loss is acceptable and what type and quantity of exercise is necessary to ensure that this loss is not exceeded?		++		+	++	++	+	+	
	1.2.4	What are the risks associated with exposure to extraterrestrial dust?	++	++		++	+		++		+
	1.2.5	What are the roles of diet and bone demineralisation on kidney stone formation and can we predict the risk of kidney stones?	+	+		+		+			

			Theme 1. Integrated view of adaptation to the space environment				Theme 2: Integrated view of CM to multiple stressors	Theme 3: Integrated view of tools and methods			
			Reco 1: Integrated survey of stressors and impact	Reco 2: Integrated survey of human interactive adaptations	Reco 3: personalised exposures and responses - individual characteristics	Reco 4: integrated risk assessment for missions	Reco 5: CM consideration at planning phases	Reco 6: optimised CM procedures and programmes	Reco 7: standard protocols and procedures for the studies on the integrative human adaptation	Reco 8: database of results from human integrative space research	Reco 9: mathematical, physical, biological and neurocognitive modelling
Immunology	1.3.1	Identification and quantification of stress factors and their impact on the immune system.	+	++	+	++			+	+	+
	1.3.2	Are immune system development, response and regulation as efficient in space (ISS/Moon/Mars) as on Earth?	+	++	+	++		+	+	+	+
	1.3.3	Consequences of long duration ( $\geq 1$ year) missions on the degree of immune-suppression.	+	++	+	+		+	+		
	1.3.4	Consequences of “chronic” immune changes during and after long-duration mission on disease.		++	+	++				+	
	1.3.5	Effect of Lunar or Mars dusts, habitat environment & other chemicals on immune performance.	++	++	+	++	+		+		
	1.3.6	Are the observed stress-dependent virus reactivation patterns linked to cancer development?		+	+					+	+
	1.3.7	Interaction between immune system and other stress-sensitive systems.		++	+	++	+	+	+		+
	1.3.8	Definition and testing of (immune targeted) countermeasures.		+			++	++	+		++

			Theme 1: Integrated view of adaptation to the space environment			Theme 2: Integrated view of countermea sures to multiple stressors			Theme 3: Integrated view of tools and methods		
			Reco 1: Integrated survey of stressors and impact	Reco 2: Integrated survey of human interactive adaptations	Reco 3: personalised exposures and responses - individual characteristics	Reco 4: integrated risk assessment for missions	Reco 5: CM consideration at planning phases	Reco 6: optimised CM procedures and programmes	Reco 7: standard protocols and procedures for the studies on the integrative human adaptation	Reco 8: database of results from human integrative space research	Reco 9: mathematical, physical, biological and neurocognitive modelling
Neurophysiology	1.4.1	Impacts of spaceflight on the senses	+	++	+	++					
	1.4.2	Impacts of spaceflight on sensorimotor performance	+	++	+	++		++	+	+	++
	1.4.3	Impacts of neurophysiological changes on spaceflight-induced decrements in neuro-behavioural performance.		++	+	++		+	+	+	++
	1.4.4	Countermeasure strategies to minimize the risks associated with neurophysiological changes during and after g transitions		+			++	++	+		+
	1.4.5	Understand the role of gravity in the development of the nervous system		+	+	+	+			+	
Nutrition and Metabolism	1.5.1	The in-flight negative energy balance	++	++	++	++		++	+	+	+
	1.5.2	Feeding behaviour	++	++	++	++		++	++	+	
	1.5.3	Metabolic stress		++	+	++		++	+	+	
	1.5.4	Micronutrients deficiency		+		+		+			
	1.5.5	Alterations of gut microflora	+	++	+	++		++	+	+	
	1.5.6	Hydro-electrolytic imbalance		+		+		+			

**Table 5: Psychology and human-machine systems - Recommendation's relevance to Key Issues (+: significant relevance, ++: high relevance)**

			Theme 1: Integrated view of adaptation to the space environment				Theme 2: Integrated view of CM to multiple stressors		Theme 3: Integrated view of tools and methods		
			Reco 1: Integrated survey of stressors and impact	Reco 2: Integrated survey of human interactive adaptations	Reco 3: Personalised exposures and responses - individual characteristics	Reco 4: Integrated risk assessment for missions	Reco 5: CM consideration at planning phases	Reco 6: Optimised CM procedures and programmes	Reco 7: standard protocols and procedures for the studies on the integrative human adaptation	Reco 8: database of results from human integrative space research	Reco 9: mathematical, physical, biological and neurocognitive modelling
Group/Team Processes	2.1.1	Maintenance of team cohesion, wellbeing and performance	+	+	++	++	+	++	++	+	
	2.1.2	Impact of reduced communication between crew and earth	++	+	++	++	+	++	++	+	
	2.1.3	Managing intra-crew differences and conflicts		+	++	++	+	+	++		
	2.1.4	Integral monitoring of crew and individual behaviour		++	++	++			++	++	++
Human-Machine Interface	2.2.1	Design of human-automation system			++		++	+	++		
	2.2.2	Adaptation to support operator state and mission goals		++			++	+	++		++
	2.2.3	Evolving, problem solving and updating during missions		++			++	+		++	
	2.2.4	Simulation and virtual/augmented reality (SVAR)					++	++	+		
	2.2.5	Robots (HRI), agents (HAI) & human-robot-agent interaction (HRAI)					++	++	+		
Skill Maintenance	2.3.1	Risks for operational effectiveness from infrequent or non-use of skills		++	+	++	++	++	++		
	2.3.2	Need for different training methods for the acquisition and maintenance of different types of skill					++	+			
	2.3.3	Use of on-board top-up training to maintain and enhance skills					+	++	+		
	2.3.4	Protection against effects of stressors on skill learning and effective long-term skilled performance	+	++	+	++	+	++	++		
	2.3.5	Management of sleep and work/rest schedules to prevent skill impairment by sleepiness and fatigue	++	++	++	+	+	+	+		++

**Table 6: Space Radiation - Recommendation's relevance to Key Issues (+: significant relevance, ++: high relevance)**

			Theme 1: Integrated view of adaptation to the space environment			Theme 2: Integrated view of countermeasures to multiple stressors		Theme 3: Integrated view of tools and methods			
			Reco 1: Integrated survey of stressors and impact	Reco 2: Integrated survey of human interactive adaptations	Reco 3: personalised exposures and responses - individual characteristics	Reco 4: integrated risk assessment for missions	Reco 5: CM consideration at planning phases	Reco 6: optimised CM procedures and programmes	Reco 7: standard protocols and procedures for the studies on the integrative human adaptation	Reco 8: database of results from human integrative space research	Reco 9: mathematical, physical, biological and neurocognitive modelling
Space Radiation Effects on Humans	3.1.1	What is the particle and dose rate dependency for acute effects?	+	++	+	++	+	+	++	++	++
	3.1.2	How is the sensitivity to acute effects modified by the space environment?	+	++	+	++			+	+	
	3.1.3	What is the effectiveness of GCR at low doses for carcinogenesis?	+	++	+	++			++	++	++
	3.1.4	Is there a risk of CNS damage from low doses of GCR?	+	++	+	++		+	++	++	++
	3.1.5	Is there a risk of non-cancer late effects from low doses of GCR?	+	++	+	++			++	++	++
	3.1.6	Is there a risk of hereditary effects from low doses of GCR?		++	+	++			++	++	++
	3.1.7	How will multi-scale mechanistic-based modelling of space radiation improve risk estimates?	+			++					++
	3.1.8	How can radiation effects be effectively mitigated?		++			++	++	++	+	++
Radiation Dosimetry	3.2.1	Experimental determination of radiation field parameters	++			++				++	++
	3.2.2	Modelling of radiation environments	++			++	+			++	++
	3.2.3	Space weather forecast	++			++	++				+
	3.2.4	Transport codes	++	+		++	+		++		++
	3.2.5	Shielding	+				++	++	++		+
	3.2.6	Individual radiation exposures	++		++	++	+	+	+		+
	3.2.7	Support to mission planning and operation					++	+			

**Table 7: Habitat Management - Recommendation's relevance to Key Issues (+: significant relevance, ++: high relevance)**

			Theme 1. Integrated view of adaptation to the space environment				Theme 2: Integrated view of CM to multiple stressors		Theme 3: Integrated view of tools and methods		
			Reco 1: Integrated survey of stressors and impact	Reco 2: Integrated survey of human interactive adaptations	Reco 3: personalised exposures and responses - individual characteristics	Reco 4: integrated risk assessment for missions	Reco 5: CM consideration at planning phases	Reco 6: optimised CM procedures and programmes	Reco 7: standard protocols and procedures for the studies on the integrative human adaptation	Reco 8: database of results from human integrative space research	Reco 9: mathematical, physical, biological and neurocognitive modelling
Microbiological quality control of the indoor environment in space	4.1.1	Define correct upper and lower thresholds for indoor environmental quality control of air, water, food and surfaces in space habitats	++	++	+		++	+	+		+
	4.1.2	Develop efficient materials and methods to prevent environmental microbial contamination in space	++				++	++	+		+
	4.1.3	Develop adequate environmental contamination monitoring (prediction, detection, identification) systems for use in space	+				++	+	+	++	++
	4.1.4	Develop materials and methods to mitigate environmental microbial contamination and its harmful effects in space	+				++	++	+		+
	4.1.5	Acquire better knowledge on microbial community (microbial ecosystem) dynamics and microbial cell evolution over time in confined manned habitats in space	++				+	+		++	++
	Life Support: management and regeneration of air, water and food	4.2.1	Develop and adopt common metrics for evaluation of different Life Support System (LSS) architectures, technologies, and their evolution					++		++	
4.2.2		Develop model-based regenerative Life Support via a system level approach					++				++
4.2.3		Further develop Life Support subsystems and components for long-duration space flight and planetary surface mission phases					++	+			+
4.2.4		Improve autonomy of LSS via monitoring and control					++				+
4.2.5		Improve LSS robustness, reliability, availability, maintainability, safety, acceptability in long-term integrated operations	+				++	+			
4.2.6		Screen and develop high performance materials for LSS					++				
4.2.7		Develop and demonstrate capabilities to exploit resources available on other planets (In-Situ Resource Utilization ISRU) for life support					++				+
4.2.8		Improve LSS architecture to increase habitability					++				++

**Table 8: Health Care - Recommendation's relevance to Key Issues (+: significant relevance, ++: High relevance)**

			Theme 1. Integrated view of adaptation to the space environment				Theme 2: Integrated view of CM to multiple stressors		Theme 3: Integrated view of tools and methods		
			Reco 1: Integrated survey of stressors and impact	Reco 2: Integrated survey of human interactive adaptations	Reco 3: personalised exposures and responses - individual characteristics	Reco 4: integrated risk assessment for missions	Reco 5: CM consideration at planning phases	Reco 6: optimised CM procedures and programmes	Reco 7: standard protocols and procedures for the studies on the integrative human adaptation	Reco 8: database of results from human integrative space research	Reco 9: mathematical, physical, biological and neurocognitive modelling
<b>Space Medicine</b>	5.1.1	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.	+	+			++	+	+		++
	5.1.2	The acute risk to health from radiation exposure, in particular solar flares - Provide on-board physical and/or pharmacological countermeasures and/or protection.	++	+		+	+	++			+
	5.1.3	Dietary and nutrition-related space flight disorders and complaints. - Provide on-board countermeasures.		+		+	+	++			
	5.1.4	Sub-optimal physical countermeasure hardware for health maintenance. - Identify and provide improved solutions to current bone and muscle loss countermeasures.					+	++	++	+	++
	5.1.5	Insufficient on-board medical imaging hardware. - Provide on-board means to maintain medical risks at an acceptable level.				+	++	+	+		
	5.1.6	Insufficient on-board smart sensors / smart devices for health monitoring & medical diagnostics. - Provide on-board means to maintain medical risks at an acceptable level.				+	++	+	+		
	5.1.7	Insufficient on-board expert systems / decision support systems for medical diagnostics. - Provide on-board means to maintain medical risk at an acceptable level.				+	++	+			
	5.1.8	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.					++	+			



			Theme 1: Integrated view of adaptation to the space environment			Theme 2: Integrated view of CM to multiple stressors		Theme 3: Integrated view of tools and methods				
			Reco 1: Integrated survey of stressors and impact	Reco 2: Integrated survey of human interactive adaptations	Reco 3: personalised exposures and responses - individual characteristics	Reco 4: integrated risk assessment for missions	Reco 5: CM consideration at planning phases	Reco 6: optimised CM procedures and programmes	Reco 7: standard protocols and procedures for the studies on the integrative human adaptation	Reco 8: database of results from human integrative space research	Reco 9: mathematical, physical, biological and neurocognitive modelling	
Space Medicine	5.1.9	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.					++	+				
	5.1.10	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.				+	++	+				
	5.1.11	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.						++	+			
	5.1.12	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.						++	+			
	5.1.13	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.						++	+			
	5.1.14	What triage decisions and medical capability limitations shall be acceptable during human exploration missions?						+	+	+		
	5.1.15	What criteria shall be accepted for the medical selection of astronaut crews for human exploration missions?		+	++			+			+	
	5.1.16	What psychological criteria shall be used for the medical selection of astronaut crews for human exploration missions?		+	++			+			+	

			Theme 1. Integrated view of adaptation to the space environment				Theme 2: Integrated view of CM to multiple stressors		Theme 3: Integrated view of tools and methods		
			Reco 1: Integrated survey of stressors and impact	Reco 2: Integrated survey of human interactive adaptations	Reco 3: personalised exposures and responses - individual characteristics	Reco 4: integrated risk assessment for missions	Reco 5: CM consideration at planning phases	Reco 6: optimised CM procedures and programmes	Reco 7: standard protocols and procedures for the studies on the integrative human adaptation	Reco 8: database of results from human integrative space research	Reco 9: mathematical, physical, biological and neurocognitive modelling
<b>Medication in Space</b>	5.2.1	Is there evidence supporting changes in drug efficacy in-flight	++	+	+			+	+		
	5.2.2	Which systems/pathways are operationally important for human spaceflight and why?	++	+	+		+	+	+		
	5.2.3	What classes of drugs should be studied as a priority to sustain the health and performance of astronauts during spaceflight?	++	+	+	+		+	+		
	5.2.4	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?	++	+	+	+		+	+		
	5.2.5	What pre-flight or in-flight tests should be conducted to avoid or assess possible side effects such as allergic reactions, problems from pharmacogenetics or influences on performance?	++	+	+	+		+	++		
	5.2.6	What tests should be conducted to assess the possible influences of medication on pre-flight and in-flight performance and sleep quality?			+	+	+	+	+		
	5.2.7	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?	++	+	+	+		+	+		
	5.2.8	What evidence exists of pharmacodynamics changes resulting from posture and physical (in)activity seen in clinical studies (bed ridden patients, sedentary people)?	++	+	+	+		+	++		
	5.2.9	What models should be used to study pharmacodynamics?	++				+		+	++	

#### 4.5. Implementing the THESEUS approach

The THESEUS recommendations suggest research orientations and a programmatic structure that would properly address the Key Issues and eventually progress towards filling the current knowledge gaps in the priority topics identified by THESEUS experts. These recommendations have to be considered as parts of an overall phased plan, with interdependencies and relative importance over the years to come. Figure 6 illustrates how THESEUS recommendations should be integrated in the future research planning at the European level (the darker the colour, the more intense activity). Following the THESEUS proposed approach would bring some medium to long-term consistency in an optimised endeavour. Furthermore, with a clear roadmap ahead, it would foster European research identity in a global context.

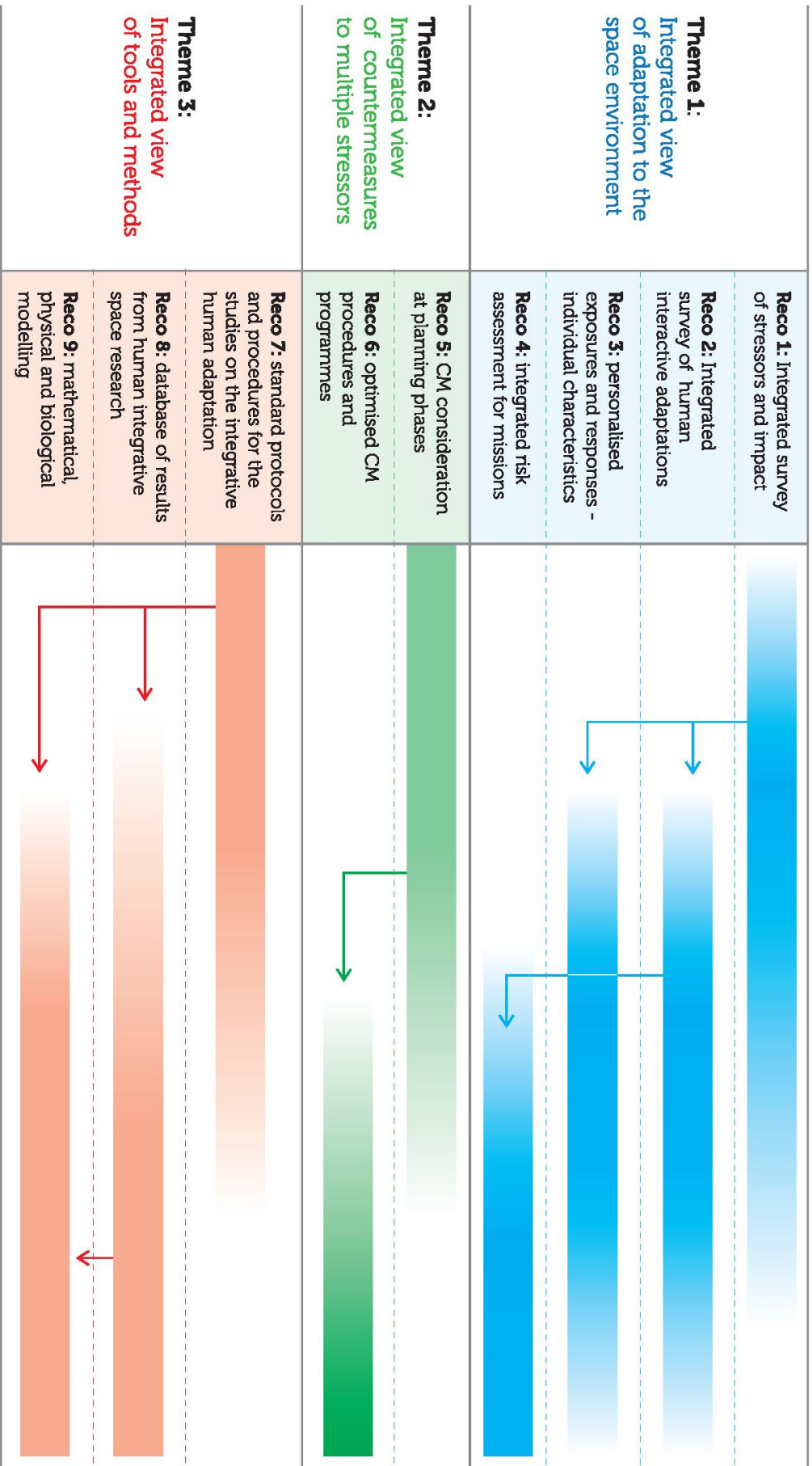
It is important to note that the THESEUS recommendations do not substitute blue skies research. Rather, THESEUS complements it by providing a coherent, integrated structure that should be implemented through **targeted calls and research solicitations** allowing mobilisation of the European scientific community around specific topics that would be increasingly programme-oriented with time.

In this context, primary implementation tools are European-wide mechanisms offered by the European Commission Horizon 2020 programme and the European Space Agency's ELIPS (European, Life and Physical Sciences in Space) and robotic exploration programmes. In addition to these programmes designed and implemented by European organisations, issues put forward by THESEUS could also be addressed through collaborative research programmes implemented by consortia of national research organisations.

Besides direct research support, an additional efficient way to address the challenges raised by THESEUS would be to foster and catalyse networking and an exchange of knowledge around these challenges. Such an approach would better structure the European scientific community and create synergies by addressing common complementary research topics.

To investigate the impacts of different elements of the space environment on human health and well-being, independently and combined, integrated experimental studies are required. This includes cellular and animal studies as well as long-term studies with astronauts as experimental subjects. Researchers should also make use of the ISS to the maximum extent possible, as living and working conditions on the ISS and its operations are especially qualified for simulating exploration missions. In addition, planetary probes to the Moon, asteroids and Mars should be used to explore the habitability of their environments and identify potential hazards for astronauts.

Complementary ground-based studies are also necessary for careful preparation of space experiments, detailed analyses of space data, and developing suitable countermeasures. These include the utilisation of existing and planned infrastructures such as the Concordia station, **:envihab** in Cologne, MELISSA in Barcelona, confinement facilities in Moscow and Krasnoïarsk, the heavy ion accelerator at GSI, Darmstadt and numerous other facilities. **:envihab** is a research facility with a completely new design and strategy aimed at studying the whole human and also taking in account its interaction with the environment. Its aim is also to link space-oriented research with terrestrial applications. As the three main challenges to maintain astronauts as healthy high performers are identical to three main tasks of the future of medicine (Prevention – Individualisation – Telecare), **:envihab** will focus on these three tasks and view astronauts as symbols for these tasks in future medicine. Thus, it is not an analogue environment for spaceflight alone, but rather a facility that links space research and terrestrial applications.



*THESEUS Roadmap – Articulation of research orientations in the future. The colour range indicates the phasing of a given recommendation – the darker the colour, the more intense activity*





Although human missions to the Moon, asteroids and Mars are not scheduled in the near future (Fig.1), the interim time of the upcoming 10 years offer the possibility for an in-depth research programme targeting a holistic approach to the responses of the human body to extraterrestrial conditions. This will then allow for a comprehensive risk assessment and development of countermeasures to mitigate risks to acceptable levels. The ALARA principle should be valid for the whole crew during the exploratory mission, thereby guarantying mission success with healthy and efficiently acting astronauts.

Implementing the recommendations of THESEUS will allow Europe to maintain and expand its role as a leader and desired partner in the international scenario of space exploration.

***Overarching Recommendation: Structure human exploration-enabling research around the themes and recommendations put forward by THESEUS, using the phased approach defined by the roadmap exercise. Programmes should be coordinated and implemented at the European level and consider direct funding, networking and exchange of knowledge as well as optimised utilisation of European research infrastructures. In this context, targeted calls and dedicated research solicitation would allow medium to long-term consistency in the process.***

## **5. Relevance to Earth Issues**

By and large, the issues and problems that humans face during missions in LEO and beyond share commonalities and applications with issues on Earth. However, the relative importance of these issues can vary dramatically. For example, the ability to predict space weather or the reliability of life support systems are critical issues for exploration missions beyond LEO while also representing opportunities to significantly improve Earth-based systems and operation without immediate risk to loss of life.

Following this idea, it must also be acknowledged that most of the research relevant to considering THESEUS Key Issues is not performed only in the context of space activities. Therefore it is crucial that space exploration-related research is continuously linked with and aware of wider research activities and that in addition to spin-offs, potential spin-in research activities are identified and exploited. This is, for instance, the case for research on improving and optimising Human-Robot interactions. This field has many applications on Earth, and it is more likely that space activities will benefit from research performed on Earth than the other way around.

However, it has to be emphasised that while some topics are intensively investigated on Earth, space exploration provides very specific conditions in terms of environments, technical constraints as well as operational and safety requirements. These specificities allow consideration of scientific and technological topics with a different angle, eventually bringing added value to Earth applications. The issue of miniaturisation of diagnostics and health monitoring equipment provides a good example of such added value.

The most salient Earth application potentials of space exploration-enabling research identified through the THESEUS project are presented below.



## 5.1 Integrated Systems Physiology

Research on integrated systems physiology aims at maintaining crew health during and after missions and ensuring that crew members are in the required physical condition to perform their tasks. Therefore, this area of research is highly relevant to health issues on Earth and is strongly related to current societal challenges such as ageing.

### ***Bones and Muscles***

The strongest translational potential of musculoskeletal research for spaceflight is the study of age-related osteoporosis and sarcopenia. Although ageing and spaceflight may involve changes in morphology and function by fundamentally different cellular and molecular pathways, they share a common feature of adaptation to changing levels in strain. Thus, studying musculoskeletal system adaptation to microgravity, and re-adaptation to 1-g parallels the context of age-related atrophy of bone and muscle tissue. Bed rest studies separate the effect of disuse from those associated with comorbidities, both in the context of fracture healing and in atrophy due to prolonged hospital stays.

### ***Heart, Lungs and Kidneys***

Heart disease is a leading cause of death in the terrestrial population, prompting significant research efforts in the domain. During space flight, a healthy population (astronauts and cosmonauts) experience significant and rapid degradation of cardiovascular performance. This provides the potential to utilise space-based research to help understand the factors that lead to cardiovascular disease on Earth.

Additionally, many people are exposed to dusty environments in the workplace, and particulate matter in the environment is a known health risk to urban populations. Further, many drugs are now delivered in aerosol form, and so a comprehensive understanding of the deposition and subsequent clearance of deposited particles is of considerable importance in both areas.

### ***Immunology***

Understanding stress-related immune challenges in space is highly relevant to the understanding of the biology of cancer immunology, the balance of inflammation and endogenous mechanisms to control it, and the lack of control (autoimmunity/allergies) in young and ageing population on Earth.

The functions of the immune system can be affected in response to environmental/living conditions, and chronic and acute stress conditions can result in a further parallel interaction between the immune system and other organ systems. As an example, stress causes neurophysiologic responses and hormone liberation which can modulate inflammation but also promote bone resorption.

### ***Neurophysiology***

Spatial disorientation and situational awareness issues are responsible for up to a quarter of all civil aviation accidents. Diminished manual flying skills during visual flight piloting is an increasing problem, especially for search and rescue helicopter pilots required to fly with diminished visual cues. A better understanding of the mechanisms underlying disorientation as well as development of physical aids (e.g., tactile situational awareness system) and countermeasures developed to aid space travellers might also be useful for commercial and military aviation.

The altered gravity environments available during spaceflight offers an additional platform to study basic neurophysiology of dexterous manipulation (eye hand coordination), balance and locomotion and vehicle control. Research in these domains can provide knowledge that serves to help patients with vestibular, neurological, and motor control problems, as well as the elderly. Knowledge gained from studying the training and rehabilitation protocols developed for use with astronauts can be transferred directly to patients with specific lesions or disorders requiring retraining or rehabilitation.



### ***Nutrition and Metabolism***

The nutritional questions related to bioastronautics research are very relevant to multiple Earth-based related health issues. The potential spin-offs are interesting from a technical point of view and also have great clinical importance. Such spinoffs encompass the increasing burden of modern chronic diseases, in which the adoption of sedentary behaviour plays a central role (i.e. the metabolic syndrome, insulin resistance, dyslipidemia, type 2 diabetes mellitus, atherosclerosis, etc.).

## **5.2 Psychology and Human-Machine Systems**

Activities performed in space are set in a very specific and peculiar environment: crew members experience continuous confinement, isolation (including potential communication delay), a hazardous external environment as well as noise, cultural differences and dependency on other crew members. Additionally, crew are at the forefront of very costly and complex endeavours imposing equally complex tasks and procedures. In this very stressful environment, performance of astronauts has to be maintained at an appropriate level.

Similar environments can be found on Earth, notably in Antarctic stations but also with oil platforms, nuclear power plants, weather stations, military units stationed in foreign countries as well as crisis/rescue situations (e.g. fire-fighting, post-earthquake rescue operations). Knowledge gained through space exploration is highly relevant to operations in these specific settings.

### ***Group/Team Processes***

A defining characteristic of space missions is that humans operate primarily as a team, yet, they also have individual needs, preferences, skills and personalities. Crews sometimes operate explicitly as teams (with common task goals) and sometimes as separate individuals within a group (with personal goals). These roles, however, can overlap and effective inter-personal interactions between crew members are critical to overall mission success.

Developing methods and tools to monitor and maintain team cohesion, well-being and performance as well as the impact of reduced communication and intra-crew differences and conflict will benefit teams that have to work in stressful and high-risk environments on Earth.

### ***Human-Machine Interface***

Space applications place extraordinary levels of reliance on technology and may drive advances in human-robot and human-agent collaborative work, interaction modalities, and concepts for interaction that involves shared physical proximity and high criticality applications.

Many current and planned work environments on Earth involve personnel interacting with increasingly automated systems. Two examples include the programme for transformation of the air traffic management system to accommodate higher levels traffic more efficiently (NextGen in the US and SESAR in Europe), and the increasing use of unmanned vehicles and robots by the military. Research on effective human-automation design will yield benefits for system efficiency and safety in these and other domains.

### ***Skill Maintenance***

Research in the field of skill maintenance has a large significance for Earth applications where naturally long breaks occur between situations requiring the use of specific skills. There is an obvious relevance for safety critical systems (e.g. nuclear power plants, chemical plants, oil platforms or refineries, hospitals and commercial aviation). Also, there are numerous complex work situations such as in process control operations, the military, aviation, and civil protection services where skills have to be maintained over long time periods and which may rarely be called upon. For some situations it may be ethically impossible to train staff under real conditions, and therefore trained in



real conditions. A particularly relevant example is when emergency rescue or disaster teams are required, or in medical emergencies when highly skilled team members are required, but the situations rarely occur.

### **5.3 Space Radiation**

Radiation levels in space pose a major challenge for human exploration activities and are currently a showstopper for a human mission to Mars. Any knowledge gain in this domain is of high relevance on Earth, especially when considering particle therapy and protection from high dose exposures for individuals and electronic systems.

#### ***Radiation Effects on Humans***

A better understanding of the acute and stochastic effects of radiation on humans is not only essential to future human spaceflight, but will also give insights into the impact of particle therapy used on Earth. Further research will determine particle therapy's impact not only healthy neighbouring tissue but also in the context of secondary tumours and non-cancer effects of radiation exposure.

New knowledge in the field of countermeasures could have a potentially high impact on mitigating the side effects from particle therapies, radiological accidents and terrorism.

#### ***Radiation Dosimetry***

Improved description of the radiation environment in space, as well as a larger degree of confidence obtained by models and simulations through optimised testing against measurements will have significant value for several terrestrial activities such as: i) monitoring and improving the reliability of spacecraft electronics, for example terrestrial and satellite telecommunication and navigation systems (GPS, mobile communication, Galileo etc.); ii) monitoring aircraft crew exposure; iii) understanding failures rates in aircraft electronics; iv) improving hadron therapy and nuclear medicine; iv) developing climate models.

Additionally, proper forecasting of solar events is an important part of the more general issue of radiation source modelling. Possible Earth applications are therefore very similar to those mentioned for the previous point. These will focus on minimising radiation driven electronic failures, avoiding potential damage to power grids, pipelines, aircraft electronics and navigation, but also on radiation protection for occupational exposure (commercial and military flights, first responders).

### **5.4 Habitat Management**

Management of complex systems is a major challenge of the 21st century. Process engineering (based on chemical engineering principles) and systems engineering (based on a hierarchical approach of control of interacting subsystems) are the clues for modern developments of industrial processes, whatever the size or functionality. When developing and installing a rationale for a specific purpose, such as life support systems for space applications (especially systems including living organisms), the methodology and approach used will be completely transferable to other applications. Controllability, modularity and reliability requirements for life support systems are excellent examples of future developments in modern industrial technology. Applications to any environmental process are straight-forward.

#### ***Microbial Quality Control of the Indoor Environment in Space***

The development of early detection and warning systems for environmental contamination and pollution has common interests for space and Earth applications. Such autonomous systems could be





used to assure healthy environments in housing and working buildings, in hospitals for fast screening of incoming patients (carrier state), for the prevention of nosocomial infections in public areas and public transport, and in pandemic control in the case of natural catastrophes. Potential medical applications are ample, including on-site infection detection and diagnosis. In addition, such systems will be of interest for continuous quality monitoring of air, water, surfaces and products in production facilities in the food and pharmaceutical industries.

In space vehicles, only a 'simplified' microbial community is able to develop (the only source is the humans, without interaction with plants, soil, animals). Space research could give a better understanding of microbial community dynamics under environmental conditions, which could be of interest for more complex Earth communities. A database of indicator organisms for expected/dominant microbial populations in confined habitats is also relevant for indoor environmental air quality control in housing and buildings on Earth in general, or for specific applications such as treatment of immune-depressed patients in hospital.

### ***Life Support: Management and Regeneration of Air, Water and Food***

Today's major studies on environment issues and sustainability, e.g., in the field of industrial ecology, mainly focus on one requirement at a time (energy consumption, water consumption or any other). However, there is a need to approach systems with a much more integrated view, taking multiple requirements into account. Although the key criteria are not necessarily the same for space and Earth applications, the methodology and metrics used for space certainly could be valuable for Earth-based systems as well. As life support system complexity (required variety) is currently not known precisely, assessment methods and tooling will surely evolve. Assessment needs and methods have to have a simultaneous and continuous approach with life support system development and its increasing level of complexity. This completely matches the methods of integrating environmental concerns in industrial developments by finding innovative solutions to complicated environmental problems, as in the emerging domain of industrial ecology.

Closed-loop waste water recycling systems could be of interest for applications on boats and cruise ships, in remote hotels (eco-tourism), remote stations for exploration and/or exploitation of remote areas (e.g. Antarctica, desert...etc.). Derived from the MELISSA life support system, there have already been applications regarding grey water treatment for hotel complexes, e.g., The Dutch company IP-Star is currently implementing these applications. Furthermore, grey water treatment can be applied to major urban developments, especially new ones, laying the path for a more sustainable way of living on Earth.

## **5.5 Health Care**

### ***Space Medicine***

With access to limited medical facilities and competencies on-board, space medicine requires that significant progress on diagnostic capability (e.g., imaging hardware, smart monitoring devices), and also on the ability to deliver appropriate health care and surgery. Miniaturisation, automation and robotics as well as reliability of equipment and power efficiency are required to bring appropriate medical operation capabilities to spacecrafts. Furthermore, it is crucial that medical skills are maintained throughout long-duration missions in order to deal with the hopefully rare emergencies in the context of a Moon or Mars mission.

### ***Drug Effects***

Research on the effects of spaceflight conditions (or analogues like bed-rest) on drug treatment, in particular pharmacokinetics, pharmaco-dynamics and side effects, will allow for a better understanding of the parameters that impact drug efficiency, and eventually improve the quality of medication on Earth.



Knowledge, experience and technological advances in the both of these fields are highly relevant to the provision of medical care in remote and/or isolated conditions (e.g., polar stations, ships, submarines) and for rescue services through better equipment in ambulances. In addition to improving autonomy of some classes of patients, advances in individual health monitoring devices will also provide clear benefits in preventing diseases or attacks or easing the management of medical emergencies. Further, advances in telemedicine will provide the opportunity to improve the ability to diagnosis and possibly treat patients in remote areas on Earth.

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## Annex 1: List of 99 THESEUS Key Issues

The 99 Key Issues identified by THESEUS are listed below by cluster; background and full details on these can be found in individual cluster reports [19-23].

### ***Cluster 1: Integrated Systems Physiology***

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#### ***EG1.1: Bones and muscles***

- Sex-based differences in the preservation of musculoskeletal tissue during space flight
- Effects of micro-gravity on musculoskeletal injuries and healing processes (ligaments and tendons, bone fracture, back pain)
- Role of genetics in musculoskeletal performance, preposition to injury and overall adaptation to micro-gravity
- Biomechanics and impact of partial gravity on the musculoskeletal system
- Effects of radiation exposure experienced during space flight on the musculoskeletal system
- Ground-based human studies
- Ground-based animal studies
- Optimise countermeasure efficiency and utilise an integrated physiology approach

#### ***EG1.2: Heart, lungs and kidneys***

- What are the inflight alterations in cardiac structure and function?
- What is the influence of spaceflight on structure and function of blood vessels?
- What level of cardiovascular function loss is acceptable and what type and quantity of exercise is necessary to ensure that this loss is not exceeded?
- What are the risks associated with exposure to extraterrestrial dust?
- What are the roles of diet and bone demineralisation on kidney stone formation and can we predict the risk of kidney stones?

#### ***EG1.3: Immunology***

- Identification and quantification of stress factors and their impact on the immune system.
- Are immune system development, response and regulation as efficient in space (ISS/Moon/Mars) as on Earth?
- Consequences of long duration ( $\geq 1$  year) missions on the degree of immune-suppression.
- Consequences of “chronic” immune changes during and after long-duration mission on disease.
- Effect of Lunar or Mars dusts, habitat environment & other chemicals on immune performance.
- Are the observed stress-dependent virus reactivation patterns linked to cancer development?
- Interaction between immune system and other stress-sensitive systems.
- Definition and testing of (immune targeted) countermeasures.

#### ***EG1.4: Neurophysiology***

- Impacts of spaceflight on the senses
- Impacts of spaceflight on sensorimotor performance



- Impacts of neurophysiological changes on spaceflight-induced decrements in neuro-behavioural performance.
- Countermeasure strategies to minimise the risks associated with neurophysiological changes during and after g transitions
- Understand the role of gravity in the development of the nervous system

#### ***EG1.5: Nutrition and metabolism***

- The in-flight negative energy balance
- Feeding behaviour
- Metabolic stress
- Micronutrients deficiency
- Alterations of gut microflora
- Hydro-electrolytic imbalance

### ***Cluster 2: Psychology and human-machine systems***

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#### ***EG2.1: Group/team processes***

- Maintenance of team cohesion, wellbeing and performance
- Impact of reduced communication between crew and earth
- Managing intra-crew differences and conflicts
- Integral monitoring of crew and individual behaviour

#### ***EG2.2: Human-machine interface***

- Design of human-automation system
- Adaptation to support operator state and mission goals
- Evolving, problem solving and updating during missions
- Simulation and virtual/augmented reality (SVAR)
- Robots (HRI), agents (HAI) & human-robot-agent interaction (HRAI)

#### ***EG2.3: Skill maintenance***

- Risks for operational effectiveness from infrequent or non-use of skills
- Need for different training methods for the acquisition and maintenance of different types of skill
- Use of on-board top-up training to maintain and enhance skills
- Protection against effects of stressors on skill learning and effective long-term skilled performance
- Management of sleep and work/rest schedules to prevent skill impairment by sleepiness and fatigue

### ***Cluster 3: Space Radiation***

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#### ***EG3.1: Space radiation effects on humans***

- What is the particle and dose rate dependency for acute effects?
- How is the sensitivity to acute effects modified by the space environment?



- What is the effectiveness of GCR at low doses for carcinogenesis?
- Is there a risk of CNS damage from low doses of GCR?
- Is there a risk of non-cancer late effects from low doses of GCR?
- Is there a risk of hereditary effects from low doses of GCR?
- How will multi-scale mechanistic-based modelling of space radiation improve risk estimates?
- How can radiation effects be effectively mitigated?

#### ***EG3.2: Radiation dosimetry***

- Experimental determination of radiation field parameters
- Modelling of radiation environments
- Space weather forecast
- Transport codes
- Shielding
- Individual radiation exposures
- Support to mission planning and operation

### ***Cluster 4: Habitat Management***

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#### ***EG4.1: Microbiological quality control of the indoor environment in space***

- Define correct upper and lower thresholds for indoor environmental quality control of air, water, food and surfaces in space habitats
- Develop efficient materials and methods to prevent environmental microbial contamination in space
- Develop adequate environmental contamination monitoring (prediction, detection, identification) systems for use in space
- Develop materials and methods to mitigate environmental microbial contamination and its harmful effects in space
- Acquire better knowledge on microbial community (microbial ecosystem) dynamics and microbial cell evolution over time in confined manned habitats in space

#### ***EG4.2: Life Support: management and regeneration of air, water and food***

- Develop and adopt common metrics for evaluation of different Life Support System (LSS) architectures, technologies, and their evolution
- Develop model-based regenerative Life Support via a system level approach
- Further develop Life Support subsystems and components for long-duration space flight and planetary surface mission phases
- Improve autonomy of LSS via monitoring and control
- Improve LSS robustness, reliability, availability, maintainability, safety, acceptability in long-term integrated operations
- Screen and develop high performance materials for LSS
- Develop and demonstrate capabilities to exploit resources available on other planets (In-Situ Resource Utilisation ISRU) for life support
- Improve LSS architecture to increase habitability



## **Cluster 5: Health Care**

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### **EG5.1: Space medicine**

- 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 acute risk to health from radiation exposure, in particular solar flares - Provide on-board physical and/or pharmacological countermeasures and/or protection.
- Dietary and nutrition-related space flight disorders and complaints. - Provide on-board countermeasures.
- Sub-optimal physical countermeasure hardware for health maintenance. - Identify and provide improved solutions to current bone and muscle loss countermeasures.
- Insufficient on-board medical imaging hardware. - Provide on-board means to maintain medical risks at an acceptable level.
- Insufficient on-board smart sensors / smart devices for health monitoring & medical diagnostics. - Provide on-board means to maintain medical risks at an acceptable level.
- Insufficient on-board expert systems / decision support systems for medical diagnostics. - Provide on-board means to maintain medical risk at an acceptable level.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- What triage decisions and medical capability limitations shall be acceptable during human exploration missions?
- What criteria shall be accepted for the medical selection of astronaut crews for human exploration missions?
- What psychological criteria shall be used for the medical selection of astronaut crews for human exploration missions?

### **EG5.2: Medication in space**

- Is there evidence supporting changes in drug efficacy in-flight
- Which systems/pathways are operationally important for human spaceflight and why?
- What classes of drugs should be studied as a priority to sustain the health and performance of astronauts during spaceflight?



- 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?
- What pre-flight or in-flight tests should be conducted to avoid or assess possible side effects such as allergic reactions, problems from pharmacogenetics or influences on performance?
- What tests should be conducted to assess the possible influences of medication on pre-flight and in-flight performance and sleep quality?
- 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?
- What evidence exists of pharmacodynamics changes resulting from posture and physical (in)activity seen in clinical studies (bed ridden patients, sedentary people)?
- What models should be used to study pharmacodynamics?

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