

SpringerBriefs in Space Life Sciences

Series Editors

Günter Ruyters

Markus Braun

Space Administration

German Aerospace Center (DLR)

Bonn, Germany

The extraordinary conditions of space, especially microgravity, are utilized for research in various disciplines of space life sciences. This research that should unravel – above all – the role of gravity for the origin, evolution, and future of life as well as for the development and orientation of organisms up to humans, has only become possible with the advent of (human) spaceflight some 50 years ago. Today, the focus in space life sciences is 1) on the acquisition of knowledge that leads to answers to fundamental scientific questions in gravitational and astrobiology, human physiology and operational medicine as well as 2) on generating applications based upon the results of space experiments and new developments e.g. in non-invasive medical diagnostics for the benefit of humans on Earth. The idea behind this series is to reach not only space experts, but also and above all scientists from various biological, biotechnological and medical fields, who can make use of the results found in space for their own research. SpringerBriefs in Space Life Sciences addresses professors, students and undergraduates in biology, biotechnology and human physiology, medical doctors, and laymen interested in space research. The Series is initiated and supervised by Dr. Günter Ruyters and Dr. Markus Braun from the German Aerospace Center (DLR). Since the German Space Life Sciences Program celebrated its 40th anniversary in 2012, it seemed an appropriate time to start summarizing – with the help of scientific experts from the various areas - the achievements of the program from the point of view of the German Aerospace Center (DLR) especially in its role as German Space Administration that defines and implements the space activities on behalf of the German government.

More information about this series at <http://www.springer.com/series/11849>

Günter Ruyters • Christian Betzel
Daniela Grimm

Biotechnology in Space

 Springer

Günter Ruyters
Former German Aerospace Center
Rheinbreitbach
Germany

Daniela Grimm
Institute of Biomedicine
Aarhus University
Aarhus C
Denmark

Christian Betzel
Institute of Biochemistry and Molecular
Biology
University of Hamburg
Hamburg
Germany

ISSN 2196-5560 ISSN 2196-5579 (electronic)
SpringerBriefs in Space Life Sciences
ISBN 978-3-319-64053-2 ISBN 978-3-319-64054-9 (eBook)
DOI 10.1007/978-3-319-64054-9

Library of Congress Control Number: 2017960963

© The Author(s) 2017

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

“Bio(techno)logy and gravity—a strange pair of terms at first glance!” With this rather surprising statement the authors of this latest booklet *Biotechnology in Space* in the series SpringerBriefs in Space Life Sciences introduce their topic. Not unexpectedly, the authors demonstrate in seven chapters following the introduction impressively that there is indeed a strong relationship between these terms: in fact, gravity has not only influenced the origin, distribution, and the evolution of life in general; also changes in gravity, especially the lack of gravity, i.e., the microgravity conditions of spaceflight, exert a marked influence on bio(techno)logical processes.

In the introductory chapter the authors describe the programmatic background and some of the early biotechnological research topics in the respective space programs of Germany and worldwide. As theoretical considerations had promised, processes such as free-flow electrophoresis, electro-cell fusion, and protein crystallization are all improved in microgravity as was shown by space experiments already in the 1970s and 1980s.

Chapters 2–4 deal in detail with the topic of protein crystallization in space. After providing some information on the theoretical background, early successes in structure elucidation by microgravity experimentation are given in Chap. 2. Chapter 3 focuses on experiments performed more recently on the International Space Station (ISS), while Chap. 4 describes the advantages of space experimentation in the context of drug discovery and drug design. The authors describe striking examples for the progress in structure determination in this rather application-oriented field of research, the results sometimes even leading to the foundation of pharmaceutical start-up companies.

In Chaps. 5–7 the focus is switched to cell biology and the role of gravity in cellular processes and cell functions. Chapter 5 provides an introduction into the topic and describes the role of gravity in several mostly human cell types. Recent findings of space experiments and accompanying ground research finally led to a hypothesis how gravity is perceived by these cells.

In Chap. 6 the authors concentrate on the more applied aspects of cell-biology research in space, namely, on tissue engineering in microgravity. Results of recent space research on cartilage, bone, endothelial cells, and thyroid cancer cells are

summarized showing that microgravity stimulates the formation of three-dimensional spheroids or tubular-like structures. The knowledge obtained from these space experiments leads to a better understanding of such process on Earth with great potential for application in the area of cell aggregate formation and pharmaceutical drug testing.

In Chap. 7 the contribution of space research in the context of cancer research is highlighted. Thyroid, breast, and skin cancer research under space conditions is described. The results obtained can be used to rethink cancer research with the aim of developing new drugs or improving cancer research strategies on Earth.

The booklet closes with an outlook on the future potential of bio(techno)logy research in space. The perspectives for future success stories in the area of protein crystallization as well as in cell biology are certainly there, especially with the further scientific utilization of the ISS in an international framework of coordination and cooperation.

Bonn, Germany
October 2017

Günter Ruyters
Markus Braun

Preface to the Series

The extraordinary conditions in space, especially microgravity, are utilized today not only for research in the physical and materials sciences—they especially provide a unique tool for research in various areas of the life sciences. The major goal of this research is to uncover the role of gravity with regard to the origin, evolution, and future of life, and to the development and orientation of organisms from single cells and protists up to humans. This research only became possible with the advent of manned spaceflight some 50 years ago. With the first experiment having been conducted onboard Apollo 16, the German Space Life Sciences Program celebrated its 40th anniversary in 2012—a fitting occasion for Springer and the DLR (German Aerospace Center) to take stock of the space life sciences achievements made so far.

The DLR is the Federal Republic of Germany's National Aeronautics and Space Research Center. Its extensive research and development activities in aeronautics, space, energy, transport, and security are integrated into national and international cooperative ventures. In addition to its own research, as Germany's space agency the DLR has been charged by the federal government with the task of planning and implementing the German space program. Within the current space program, approved by the German government in November 2010, the overall goal for the life sciences section is to gain scientific knowledge and to reveal new application potentials by means of research under space conditions, especially by utilizing the microgravity environment of the International Space Station (ISS).

With regard to the program's implementation, the DLR Space Administration provides the infrastructure and flight opportunities required, contracts the German space industry for the development of innovative research facilities, and provides the necessary research funding for the scientific teams at universities and other research institutes. While so-called small flight opportunities like the drop tower in Bremen, sounding rockets, and parabolic airplane flights are made available within the national program, research on the ISS is implemented in the framework of Germany's participation in the ESA Microgravity Program or through bilateral cooperations with other space agencies. Free flyers such as BION or FOTON satellites are used in cooperation with Russia. The recently started utilization of Chinese spacecrafts like Shenzhou has further expanded Germany's spectrum of flight

opportunities, and discussions about future cooperation on the planned Chinese Space Station are currently underway.

From the very beginning in the 1970s, Germany has been the driving force for human spaceflight as well as for related research in the life and physical sciences in Europe. It was Germany that initiated the development of Spacelab as the European contribution to the American Space Shuttle System, complemented by setting up a sound national program. And today Germany continues to be the major European contributor to the ESA programs for the ISS and its scientific utilization.

For our series, we have approached leading scientists first and foremost in Germany, but also—since science and research are international and cooperative endeavors—in other countries to provide us with their views and their summaries of the accomplishments in the various fields of space life sciences research. By presenting the current SpringerBriefs on muscle and bone physiology we start the series with an area that is currently attracting much attention—due in no small part to health problems such as muscle atrophy and osteoporosis in our modern aging society. Overall, it is interesting to note that the psycho-physiological changes that astronauts experience during their spaceflights closely resemble those of aging people on Earth but progress at a much faster rate. Circulatory and vestibular disorders set in immediately, muscles and bones degenerate within weeks or months, and even the immune system is impaired. Thus, the aging process as well as certain diseases can be studied at an accelerated pace, yielding valuable insights for the benefit of people on Earth as well. Luckily for the astronauts: these problems slowly disappear after their return to Earth, so that their recovery processes can also be investigated, yielding additional valuable information.

Booklets on nutrition and metabolism, on the immune system, on vestibular and neuroscience, on the cardiovascular and respiratory system, and on psycho-physiological human performance will follow. This separation of human physiology and space medicine into the various research areas follows a classical division. It will certainly become evident, however, that space medicine research pursues a highly integrative approach, offering an example that should also be followed in terrestrial research. The series will eventually be rounded out by booklets on gravitational and radiation biology.

We are convinced that this series, starting with its first booklet on muscle and bone physiology in space, will find interested readers and will contribute to the goal of convincing the general public that research in space, especially in the life sciences, has been and will continue to be of concrete benefit to people on Earth.

Bonn, Germany
Bonn, Germany
July 2014

Günter Ruyters
Markus Braun



DLR Space Administration in Bonn-Oberkassel (DLR)



S133E010451

The International Space Station (ISS); photo taken by an astronaut from the space shuttle Discovery, March 7, 2011 (NASA)



S122E008223

Extravehicular activity (EVA) of the German ESA astronaut Hans Schlegel working on the European Columbus lab of ISS, February 13, 2008 (NASA)

Contents

1	Biotechnology, Cell Biology and Microgravity	1
1.1	Introduction	1
1.2	Programmatic Background and Early Research Topics.....	3
1.2.1	Free-Flow Electrophoresis.....	4
1.2.2	Electro Cell Fusion	5
1.2.3	Protein Crystallization in Space.....	6
1.2.4	Cell Biology in Space	8
1.3	Perspectives	9
	References.....	10
2	Protein Crystallization in Space: Early Successes and Drawbacks in the German Space Life Sciences Program	11
2.1	Introduction: Nobel Prize for Clarification of Ribosome Structure.....	11
2.2	Some Thoughts on the Theoretical and Methodological Background	13
2.3	Early Successes of Structure Elucidation as Obtained in the German Space Life Sciences Program.....	19
2.3.1	The Structure and Function of Photo System I	19
2.3.2	The Crystallization of Archaea Surface Proteins.....	20
2.3.3	Bacteriorhodopsin: A Promising Compound for Biotechnological Applications.....	20
2.3.4	Mistletoe Lectin as an Agent in Immune Stimulation and Cancer Treatment	21
2.3.5	Mirror-Image RNA Molecules.....	23
2.4	Perspectives for Protein Crystallization in Space	23
	References.....	24

- 3 Protein Crystallization on the International Space Station ISS 27**
 - 3.1 Hardware Constructed and Adapted to ISS Crystallization Experiments 27
 - 3.2 Long Term Crystallization Experiments: Results, Advantages and Considerations 32
 - References 36
- 4 Drug Design 41**
 - 4.1 Protein Crystallography and Drug Discovery 41
 - 4.2 Impact of Microgravity Crystallization on Structure Determination and Drug Design 42
 - References 54
- 5 Cell Biology in Space 59**
 - 5.1 Introduction 59
 - 5.2 Human Adult Retinal Pigment Epithelium Cells 60
 - 5.3 Lymphocytes Cultured Under Conditions of Microgravity 61
 - 5.4 Vascular Cells in Space 63
 - 5.5 Chondrocytes and Bone Cells 64
 - 5.6 Cancer Cells Cultured in Microgravity 66
 - 5.7 Hypothesis on How Gravity Is Perceived by Human Cells: The Tensegrity Model—How Unspecialized Human Cells Might Sense Gravity 68
 - References 69
- 6 Tissue Engineering in Microgravity 73**
 - 6.1 Introduction 73
 - 6.2 Tissue Engineering in Simulated Microgravity 75
 - 6.2.1 Cartilage 75
 - 6.2.2 Thyroid Cancer Spheroids 76
 - 6.2.3 Bone 77
 - 6.2.4 Endothelium 78
 - 6.3 Tissue Engineering in Real Microgravity 79
 - 6.3.1 Cartilage 80
 - 6.3.2 Thyroid Cancer Spheroids 80
 - References 81
- 7 Cancer Research in Space 87**
 - 7.1 Introduction 87
 - 7.2 Contribution of Space Research to Cancer Research 88
 - 7.3 Studies on Thyroid Cancer 91
 - 7.3.1 The Cytoskeleton May Act as a “Gravisensor” 93
 - 7.3.2 The FTC-133 Cell Line Is More Suitable for Space Experiments 93
 - 7.3.3 The First Space Flight of Thyroid Cancer Cells: 1- μ g vs. 8- μ g 94
 - 7.3.4 Alteration of the Extracellular Matrix 94
 - 7.3.5 Changes in Cell Signaling 95

- 7.4 Studies on Breast Cancer 95
 - 7.4.1 Microgravity Triggers Rearrangement of the Cytoskeleton 97
 - 7.4.2 Formation of MCSs 97
 - 7.4.3 Effects of μg on the Extracellular Matrix 98
 - 7.4.4 Tumoroids and Histoids: Heterogeneous Breast Tumor Models 99
- 7.5 Studies on Skin Cancer: Malignant Melanoma 99
- References 100
- 8 Outlook: Future Potential of Biotechnology Research in Space. 107**
 - 8.1 Perspectives for Protein Crystallization in Space 107
 - 8.2 Perspectives for Cell Biology Research in Space 108

Contributors

Christian Betzel Laboratory for Structural Biology of Infection and Inflammation, Institute of Biochemistry and Molecular Biology, University of Hamburg, Hamburg, Germany

Markus Braun Space Management, German Aerospace Center (DLR), Bonn, Germany

Marcus Krüger Clinic for Plastic, Aesthetic and Hand Surgery, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany

Arayik Martirosyan Laboratory for Structural Biology of Infection and Inflammation, Institute of Biochemistry and Molecular Biology, University of Hamburg, Hamburg, Germany

Günter Ruyters Space Management, German Aerospace Center (DLR), Bonn, Germany

Markus Wehland Clinic for Plastic, Aesthetic and Hand Surgery, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany

Johann Bauer Max-Planck-Institute of Biochemistry, Martinsried, Germany

Daniela Grimm Institute of Biomedicine, Pharmacology, Aarhus University, Aarhus, Denmark