Space 4 Healthcare

New Space Economy

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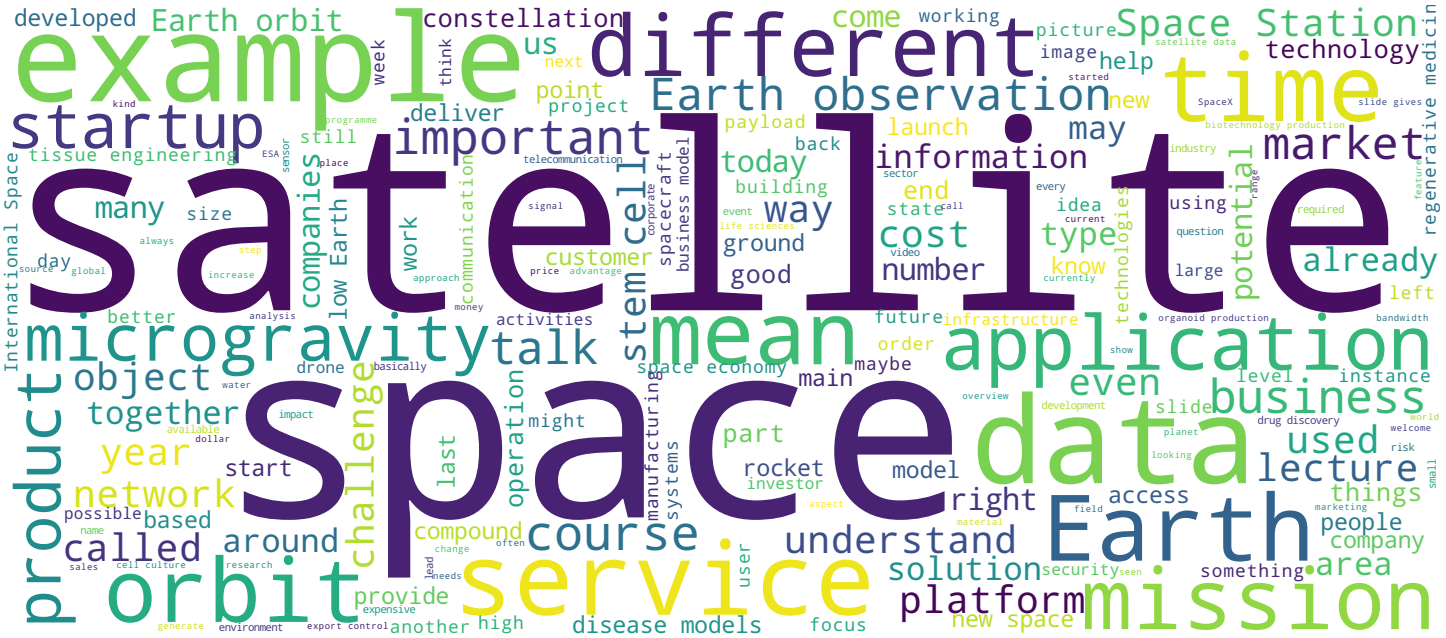
(Director: Prof. Dr. Dr. Oliver Ullrich)



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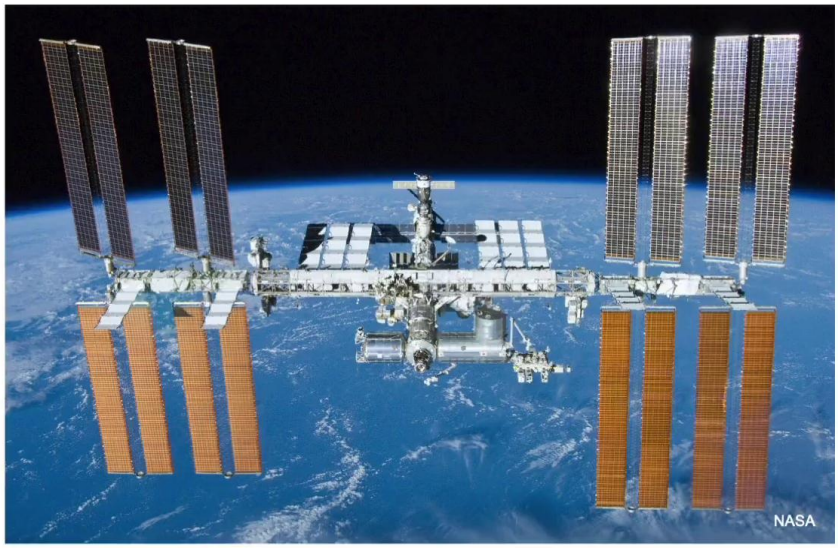
Video

Microgravity for biotechnology production & applications



Hello everybody and welcome to this lecture. I'm Cora Thiel, and I work at the University of Zurich as a Scientific Group Leader of the Cell Biology, Gravitational Biology, and Biomechanics Group. Additionally, I am the Coordinator of Space Life Sciences at the UZH Space Hub. In this lecture today, I will talk about how microgravity can be used for biotechnology production and applications.

Notes

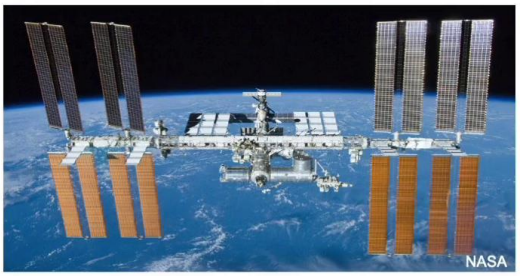
Summary

0m 05s

Microgravity platforms for biotechnology production applications

- Drop tower
- Parabolic flights
- Suborbital flights
- Sounding rockets

- **Low Earth Orbit (LEO)**
  - International Space Station (ISS)
  - Cube sats



This slide gives an overview of the different microgravity platforms. The drop tower allows experiment times of up to nine seconds. On parabolic flights, 22 seconds of microgravity time can be achieved, while on suborbital flights and sounding rockets, the microgravity time is in the range of several minutes. If longer exposure times, like days or weeks to microgravity are needed, the International Space Station or even CubeSats are the platforms of choice.

Notes

Summary

0m 31s

Environmental conditions in Low Earth Orbit (LEO)

- Space environment
  - Space radiation, extreme temperatures, vacuum, microgravity
- In microgravity various phenomena known on Earth are significantly altered like:
  - Density gradients
  - Gravity driven convection
  - Reduced surface / interfacial tension
  - Buoyancy
  - Hydrostatic pressure
  - Sedimentation

What are the environmental conditions in low Earth orbit? The space environment is a very special and hostile environment where you'll find radiation, extreme temperatures, vacuum, and microgravity. For this talk, I will only focus on the aspect of microgravity. In microgravity, various phenomena, known on Earth, are significantly altered like density gradients, gravity driven convection, reduced surface and interfacial tension, buoyancy, hydrostatic pressure, and sedimentation.

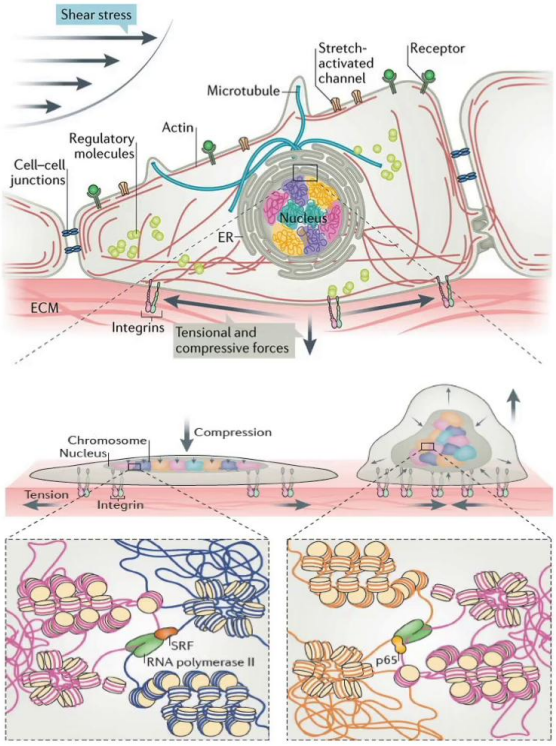
Notes

Summary

1m 05s

Why Space?

- Advantage of key attributes of microgravity
- Investigation of features of terrestrial life & physical processes that can not be manipulated on Earth
- Microgravity alters many observable phenomena in physical and life sciences like e.g.
  - global alteration in gene expression
  - 3 dimensional aggregation of cells into tissue like architecture



Uhler et al., 2017

These characteristics are also the advantage of microgravity. We can perform investigations of features that cannot be manipulated on Earth. Microgravity alters many observable phenomena in physical and as well in life sciences. On the right side, you see a cell that is attached to a surface, sensing and reacting to different stimuli like, for example, shear stress or gravity. The cell and its organelles are highly structured. For example the chromosomes as nucleus, are not randomly distributed, but each chromosome has its very specific position. The nucleus is connected via the cytoskeleton to the cell membrane, and environmental stimuli like changes in gravity level can be directly transmitted to the inside of the cell. This leads them to a rearrangement of the chromosomal positions and to global alterations in gene expression. A big advantage of cells growing in microgravity, is that they tend to aggregate and grow three-dimensional, and form tissue like structures that resemble much more the physiological conditions inside the body, compared to a 2D cell culture.

Notes

Summary

1m 41s

Microgravity for biotechnology production & applications

- **Biomanufacturing**
  - Pharmacology
  - Protein crystallization
  - Antibody production
- **Disease Models and Aging**
  - Tissue / organ on a chip
- **Tissue Engineering & Regenerative Medicine**
  - Stem cells
  - 3D Bioprinting
  - Organoids

Therefore, microgravity is very well suited for biotechnology production and applications. In this lecture, I want to focus on three topics: biomanufacturing with pharmacology, protein crystallisation and antibody production, disease models and ageing with tissues and organs on a chip, and third, tissue engineering and regenerative medicine including stem cells, 3D bioprinting, and organoids production.

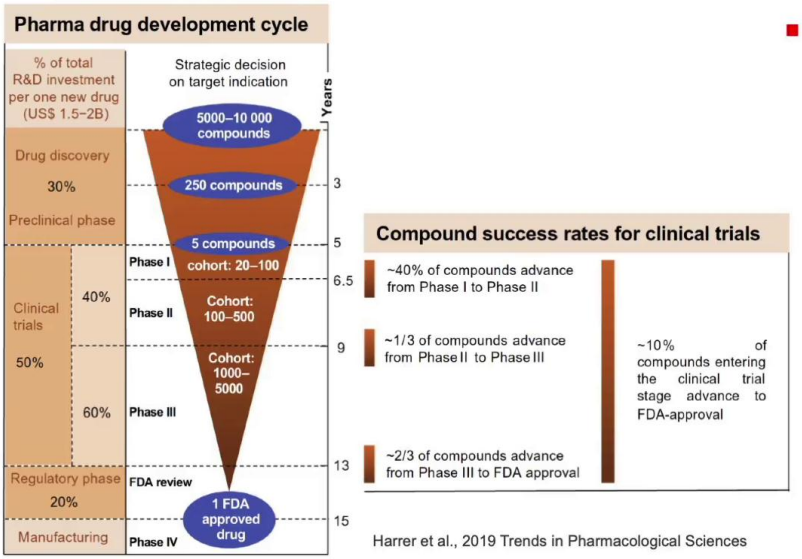
Notes

Summary

3m 01s

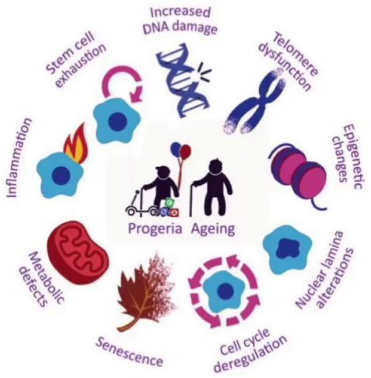
Challenges on Earth

- **Biomanufacturing**
- Pharmacology & Drug discovery



Harrer et al., 2019 Trends in Pharmacological Sciences

- **Disease models & Aging**
- Knowledge transfer from (animal) models is often difficult
- Aging research requires long experiment times



Carrero et al., 2016 Disease Models & Mechanisms

What are the challenges on Earth? The pharmaceutical drug discovery process is long, complex, and very expensive, and there's a high failure rate. A study usually starts with several thousand compounds, and then when entering the clinical trials, only a few compounds are left and only 10% of the compounds that enter the clinical trial stage advance to FDA approval. In the picture shown on the left, the study starts with 5,000-10,000 compounds, and after five years, only one compound reaches FDA approval. Also, disease and ageing research using cell culture and animal models is very cumbersome. Research requires long experiment times, and the knowledge transfer from models to human is often very difficult.

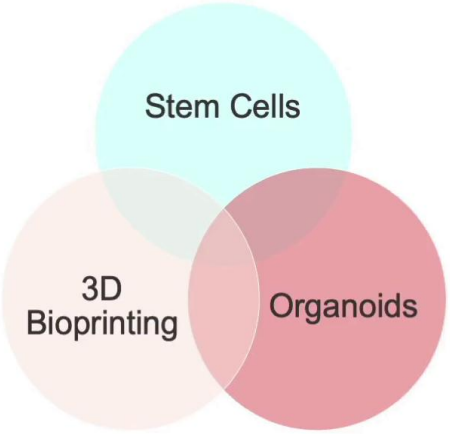
Notes

Summary

3m 29s

Challenges on Earth

- **Tissue Engineering & Regenerative Medicine**
  - Organ shortage
  - Aging population
  - Demand for cell therapy
  - Demand for improved disease models
- Limitations of organoid production on Earth due to gravity
  - Scaffolds are required



Also, in the area of tissue engineering and regenerative medicine, there are big challenges. An organ shortage exists and patients often have to wait for many, many years for an organ donation and transplantation. However our population is getting older, and there is an increased need for organ donations as well as for cell therapy and together with this, for improved disease models. Organoid production is a rapidly growing field and could be the solution for these challenges. However, there are limitations of organoid productions on Earth. Due to the gravity environment, three-dimensional growths of organoids is impaired and scaffolds are required as supportive structures.

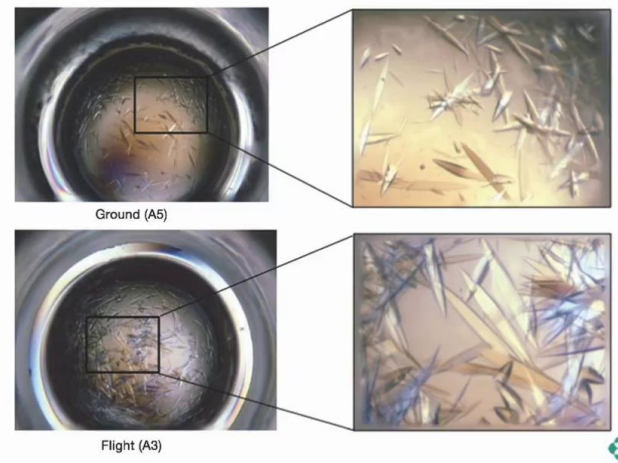
Notes

Summary

4m 22s

The Solution – Production in Space

- Biomanufacturing
  - Pharmacology & Drug discovery



- Protein crystallization for high resolution 3D protein structures to identify protein function as drug or drug target
- Advantage in microgravity:
  - absence of buoyancy-induced convection, no sedimentation, random diffusion
  - Leads to slowed down movement of protein molecules
- Substantially improved crystal growth:
  - larger, well ordered, high diffraction resolution, Rare crystalline structures (polymorphs)
- Results in increased:
  - drug efficacy, serum half life, concentration

Production in space allows to circumvent those problems. With respect to pharmacology and drug discovery, protein crystallisation is an important step to identify protein functions as drug or drug target. The environmental conditions in microgravity allow substantially improved crystal growth, and compounds could already be identified with an increased drug efficiency, with an increased serum half-life and increased concentrations.

Notes

Summary

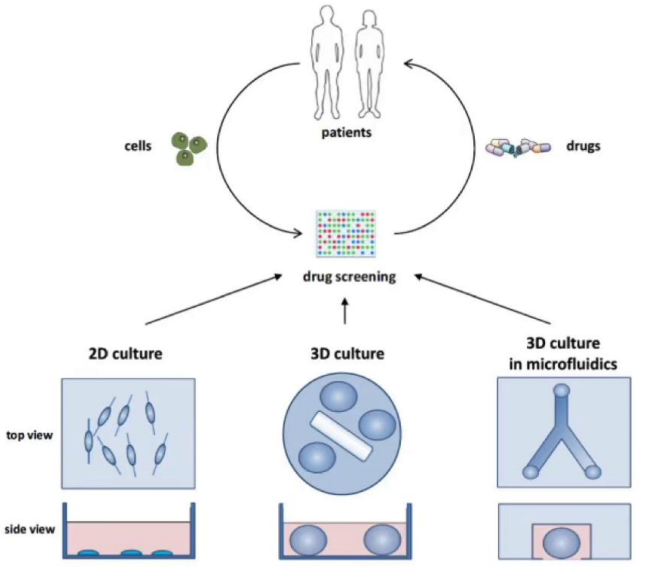
5m 07s

The Solution – Investigations in Space

- Disease Models and Aging
  - Tissue / organ on a chip
  - Drug development
  - Disease modelling
  - Personalized medicine

  - Defined flow rate
  - Size, shape, stiffness
  - Cellular co-culture
  - Exposure to substances like drugs

  - In use for
    - Cardiac dysfunction
    - Kidney function
    - Bone function



Friese et al., The Convergence of Stem Cell Technologies and Phenotypic Drug Discovery, Cell Chemical Biology (2019), https://doi.org/10.1016/j.chembiol.2019.05.007

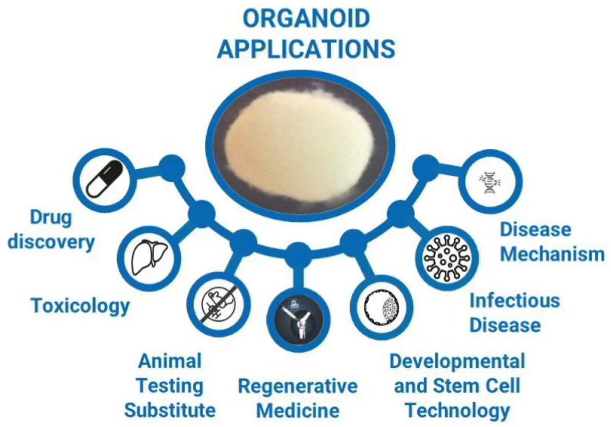
Also for disease models and ageing research, investigations in space are beneficial. Tissue and organ on a chip platforms represent new opportunities to grow tissue like structures in 3D and to expose these structures to different substances and conditions. These platforms have been already used for studies of cardiac dysfunction, kidney and, bone function.

Notes

Summary

5m 39s

The Solution - 3D Organoids Production in Space



Advantages over 2D cell culture and animal testing
Close human in vivo physiological conditions

Project performed by: UZH & Airbus Defence and Space

What is an organoid?

- Multicellular 3D structure
- Derived from stem cells
- Multiple cell types
- Self organization
- Specialized organ function

Indispensable tool for studies in

- Drug discovery
- Toxicity
- Regenerative medicine
- Substitute for animal testing
- And more

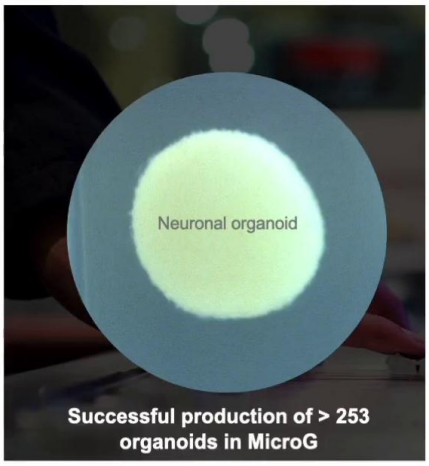
There is currently a big effort to address the wide field of tissue transplantation and personalised medicine with organoids. I would like to give you here a short overview about what is an organoid, and what are the possible application fields for organoids. Organoids are multicellular 3D structures that derived from stem cells. They develop into complex structures made out of multiple cell types and show self organisation as well as specialised organ function. This means they are organ like. Organoids provide an enormous application potential and can be applied for drug discovery, toxicity testing of substances, substitution of animal testing, regenerative medicine, and many more.

Notes

Summary

6m 04s

Microgravity as a Tool



By using **microgravity** as a tool for **tissue production** from **stem cells**, we can

- Produce efficiently and robustly organoids without additives or matrix structures normally required on Earth
- Enable early testing of potential drugs on human organoids
- Reduce cost of pre-clinical tests by a factor of 5-10x
- Start research on personalized drugs
- Start research to repair damaged organs generated from personal stem cells

Project performed by: UZH & Airbus Defence and Space

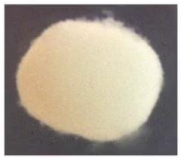
By using microgravity as a tool for tissue production from stem cells, it is possible to produce efficiently and robustly organoids without additives or matrix structures, normally required on Earth. Enable early testing of potential drugs on human organoids, reduce costs of preclinical tests by a factor of 5-10, and we can start research on personalised drugs as well as research to repair damaged organs generated from personal stem cells.

Notes

Summary

6m 53s

The Underlying Magic



Ideal size for vascularization by the transplant recipient

Human organoid production in space is 100% successful !

- **Natural human organoids** = No additives / matrix structures etc required, because of the microgravity environment – highly efficient and robust organoid production
- **Production of many large and homogeneous "organoid units" in space**

	Cartilage	Bone	Fat	Liver	Neurons
Organoid formation ISS Flight	✔	✔	✔	✔	✔
Organoid formation Ground control (2D)	x	x	x	x	x

Project performed by: UZH & Airbus Defence and Space

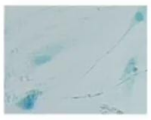
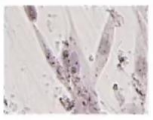
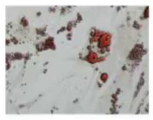
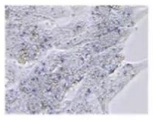
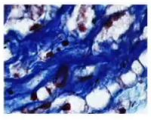
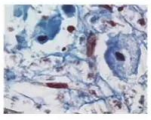
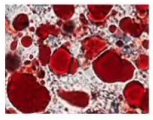
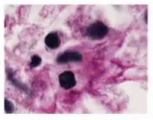
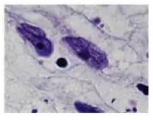
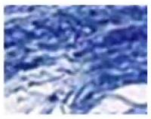
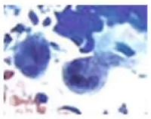
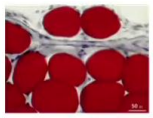
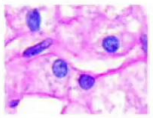
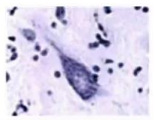
During our pilot study in 2020, we developed the necessary protocols and executed successfully our space experiment, where we sent 253 samples to the International Space Station. Human stem cells derived from bone marrow, were cultivated with specifically defined cell culture media that drive the stem cell development into tissue specific organoids. In our first attempt, we wanted to generate five different human tissues. The analysis of the samples showed that in each of the 253 cell containers, we obtained complex organoids. This means our project was 100 percent successful. What is also very important, the organoid structures produced in microgravity are 100 percent natural, that means no additives or matrix structures are required for the formation in space compared to Earth. We therefore developed a highly efficient and robust organoid production system. As you can see in the picture on the left side, the organoids reached diameters of up to 1.5 millimetre, which is an ideal size for transplantation with respect to vascularization. On Earth, organoids produced with artificial scaffolds are much smaller, and usually have sizes of below 0.5 millimetres.

Notes

Summary

7m 28s

Characteristic tissue differentiation in microgravity

	Cartilage	Bone	Adipose (Fat)	Liver	Neurons
Ground control (2D)					
Tissue differentiation ISS Flight					
«Human Tissue» Textbook Reference					

Ground controls show no or minor differentiation

Project performed by: UZH & Airbus Defence and Space

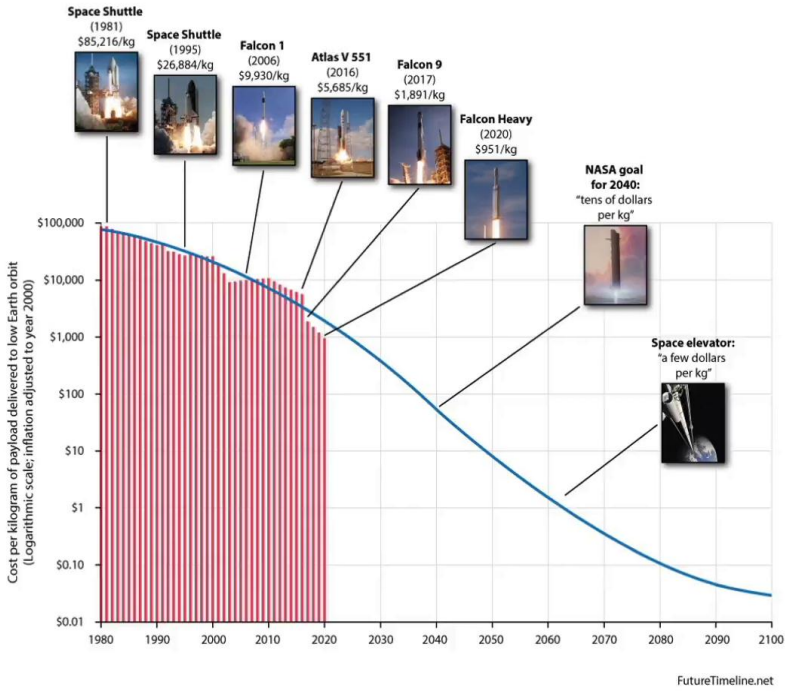
This slide gives an overview of our results. For all tissues you see a clear difference between the 2D ground control, with no or only minor differentiation, and the ISS samples that show exactly the features of the textbook references, which are displayed in the last row.

Notes

Summary

8m 51s

Launch costs to low Earth orbit, 1980-2100



- Constantly decreasing costs
- Long-term goal LEO accessibility for tens of dollars per kilogram by 2040

You might ask yourself if research or production in space is expensive. This picture shows that the launch costs are constantly decreasing with a long term goal that by 2040, the launch of one kilogramme will only cost tens of dollars.

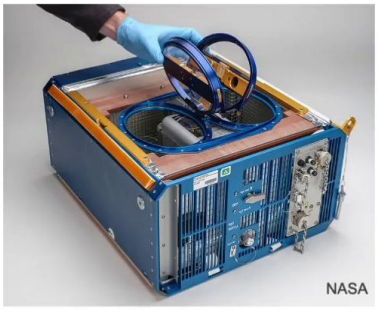
Notes

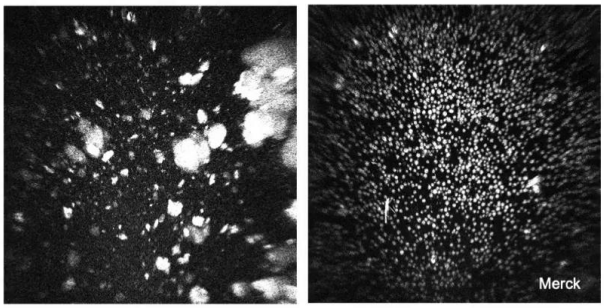
Summary

9m 10s

Pharma Companies in Space - Examples

- Amgen
  - Efficacy testing of drugs for osteoporosis in mice on board the ISS
- Novartis
  - Investigation of muscle atrophy in rodents
- Merck
  - Crystallisation of therapeutic monoclonal antibody
- Space Pharma
  - lab-on-chips technology to perform crystallization experiments under microgravity





Sources: ISSNationalLab.org & spinoff.nasa.gov, Amselem, 2019, Pharm Res

This slide gives you some examples of research and production applications of pharma companies in space. It includes drug testing, crystallisation of therapeutic antibodies, disease models, and lab on a chip technology.

Notes

Summary

9m 29s

Future Perspectives

The Center for the Advancement of Science in Space (CASIS)

- ISS National Lab Research Announcement: “In Space Production Applications Tissue Engineering and Biomanufacturing” (CASIS in coordination with NASA)
- NASA is taking more steps to support new commercial space stations in low Earth orbit
- Axiom Space, Inc. plans to build a commercial space station (2024-2028) for research and manufacturing

What are the future perspectives for biotechnology production and applications in space? Recently, the ISS National Lab made a research announcement for in-Space production applications like tissue engineering and biomanufacturing. Additionally, NASA is taking more steps to support new commercial space stations in low Earth orbit. The company, Axiom Space Inc., plans to build a commercial space station between 2024-2028, for research and manufacturing.

Notes

Summary

9m 46s

Conclusion

Students learn to understand that:

- The “new space” environment will enable easy and affordable access to space
- Microgravity is a unique environment with (almost) endless possibilities
- Space economy is of high scientific and economic value with respect to
  - biomanufacturing, disease models & aging and tissue engineering & regenerative medicine

With this slide, I want to summarise and conclude my lecture. I showed that the new space environment will enable easy and affordable access to space, that microgravity is a unique environment with almost endless possibilities, and that space economy is of high scientific and economic value with respect to biomanufacturing, disease models and ageing, as well as tissue engineering and regenerative medicine.

Notes

Summary

10m 24s

Conclusion

With this, I would like to end my talk, and I thank you for your attention.

Notes

Summary

10m 51s