SPECIAL REPORT

LIFE SCIENCES IN MICROGRAVITY

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KAYSER ITALIA

MUSCLE ATROPHY IN SPACE

BY ANDREA GINI

The human body has adapted over millions of years to work and operate within the gravity field. The musculoskeletal system is sized to act, jump, grip, grasp, carry loads, move, maintain balance, and use and define all the motor control strategies which are necessary for a safe life on Earth.

The absence of gravity makes working in a spacecraft physically undemanding. In a weightless environment, very little muscle contraction is needed to support the body and move around. Such effortless motion results in weakening of calf muscles, quadriceps and the muscles of the back and neck in a process called atrophy. An astronaut can experience a muscle mass loss as high as 5% a week.

aRED (top) and CHIBIS (bottom). aRED will be used in combination with Kayser Italia's ELITE S2 for the BICE Experiment selected by ESA in ILSRA-2009.
Credits: NASA

Even the heart is affected by atrophy. In space, blood pressure is about 100 mmHg throughout the body, with no differential between head and feet. When bodily fluids redistribute themselves in the new environment, astronauts appear to have swollen faces and thin legs. The lack of blood pressure gradient means less blood is needed, causing the body to excrete about 22% of its blood volume. The heart doesn't need to pump as hard to distribute the blood, therefore it atrophies

If one could remain in space forever, muscle loss would not be a problem, but when crewmembers return to Earth their bodies have to readjust to gravity. Most space adaptations appear to be reversible, but the rebuilding process is not necessarily easy. While blood volume is typically restored within a few days, muscle recovery takes about a month. Bone loss is even more problematic, taking up to three years to recover.

ZERO-G EXERCISE

The only way to minimize muscle atrophy in space is through intensive strength training exercise – up to 2.5 hours a day. But exercising in space is only effective if it entails some gravity-like resistive force. On ISS, this resistance is provided by strapping an astronaut to a treadmill with bungee cords. The straps are not particularly comfortable, so astronauts can only exercise with loads of 60-70% of their body weight. Astronauts can include squats, dead lifts, heel lifts, and various presses and curls in their routines using the Advanced Resistive Exercise Device (aRED), which can provide more than 270kg of resistance.

Even though these machines are partially effective in mitigating the effects of weightlessness on muscles, increasing loads on muscles and bones is not enough without taking care of fluid flows. Chibis aims to do just that. It is a Russian below-the-waist suit that applies suction to the lower body, simulating a gravity-like stress to the body's cardiovascular system. In the days before returning home, cosmonauts perform a preparatory training in the suit consisting of drinking 150-200 milliliters of fluids, followed by a sequence of progressive regimes of negative pressure (from -15 to -30 mmHg) for five minutes each while shifting from foot to foot at 10-12 steps per minute. This protocol induces the body's circulatory system to interpret the pressure differential between upper and lower body as a gravity-like force pulling the blood (and other liquids) down. The exercise prevents much of the loss of cardiovascular function and of muscle, and may also be effective in reducing bone loss.

INVESTIGATING UPPER LIMB ATROPHY

BY ANDREA GINI

The muscles of the upper limbs are also affected by the lack of gravity. The Italian Space Agency, with support from Kayser Italia, is currently promoting a wide program of microgravity experiments on the upper limbs. We contacted Dott. Valfredo Zolesi, president of Kayser Italia and principal investigator of the Hand Posture Analizer (HPA) facility, to know more about the research in this field.

"The upper limbs are the principal means of locomotion for crews living in a space station," explains Zolesi. "Fatigue can have a significant effect on the hands, affecting both on-board activities and EVAs. These are the main reason to study and characterize this phenomenon."

Kayser Italia developed Hand Posture Analyzer (HPA), a facility designed to investigate astronauts' upper limb performance during space missions. "The experiment consists of a Hand Grip Dynamometer (HGD) and a Pinch Force Dynamometer (PFD), which are crew operated tools designed to measure respectively hand grip and pinch force application."

The facility allows the ISS crew to run a protocol called CHIRO ("Crew's Health: Investigation on Reduced Operability"), to "investigate how hand grip control and precision lateral pinch force are influenced by reduced gravity, and to quantify the adaptive normalization during the mission."

Following on-screen instructions, the astronaut is requested to grip the HGD or to pinch the PFD as strongly as possible, exerting the so-called Maximum Voluntary Contraction (MVC), and holding it for a certain interval. The tests alternates between providing on-screen feedback on gripping/pinching strength to the subject and providing no feedback except the subject's own proprioceptive sense..

By conducting pre-flight, in-flight, and post-flight testing, the experiment enables researchers to characterize hand performance before, during, and after an ISS increment. "Over a six month mission, the hand grip MVC tends to decrease about 45%, while the pinch MVC remains stable," explains Zolesi. "There is no adaptation with time, no recovery, and HGD-MVC values decrease continuously in weightless conditions, a serious issue in missions longer than six months."

The HPA also features an instrumented glove that records how the hand reaches for and grasps an object. "The glove has 15 degrees of freedom, allowing the study of the position of single phalanxes," says Zolesi. "This is coupled with an inertial platform on the wrist, which measures motion control strategies during grasping and reaching tasks enabling the study of alteration in cognitive processes."

The experiment measures how the subject reaches for an object, grasps it, and moves it to a position indicated on-screen. "When we reach for an object, our brain evaluates the distance and weight of the object. The arm moves taking into account these evaluations. As soon as the hand approaches the target, the wrist decelerates and adjusts the grip in order to complete the action."

With the lack of gravity, hands experience a disabling effect. "The capability of hand grip is highly influenced by microgravity. This situation resembles the pathology of muscle atrophy or spinal cord injury. In this sense, if Earth is a normal environment for disabled people, Space is a disabling environment for normal people," concludes Zolesi.

The major application of this research is the ergonomics of crew user interfaces, but the same principles can be applied in rehabilitation of subjects on the ground with local trauma or central nervous system disorders. "A subset of the facility has been used in clinic on more than 200 elderly patients, and also to study the progress in Carpal Tunnel and in the Trapezium-Metacarpal Arthrosis."

(1) Zolesi et al, 2001. Hand Posture Analyzer (HPA): a set of portable instruments for upper limb posture analysis on the International Space Station, presented at AIAA Conference & Exhibit on ISS Utilization, Cape Canaveral, 2001.

(2) Zolesi et al, 2004. Short term microgravity effect on isometric hand grip and precision pinch force with visual and proprioceptive feedback, COSPAR.

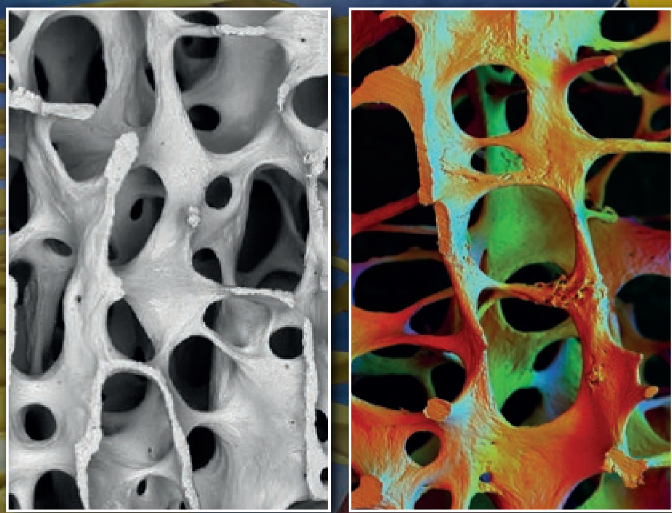
Italian astronaut Roberto Vittori uses the Hand Grip Dynamometer (HGD) of Kayser Italia's Hand Posture Analyzer (HPA). The HGD is a precision tool designed to measure hand grip's Maximum Voluntary Contraction (MVC).
Credits: NASA

MICROGRAVITY BONE LOSS ILLUMINATES OSTEOPOROSIS ORIGINS

BY TEREZA PULTAROVA

Microgravity and aging: what do they have in common? At first sight not much, but under the microscope or through modern analytical methods like quantitative computed tomography, the similarities become striking. Starting with the Gemini and Apollo missions in the 1960s, doctors noticed in post-flight exams that astronauts showed higher calcium levels in their urine and measured decreased mineral density in their bones. Does it ring a bell? Yes: decrease in bone density is a symptom of osteoporosis, a disease that affects more than 50% of the population over 50 years old.

Whereas osteoporosis is primarily caused by hormonal changes accompanying aging, in microgravity induced bone loss the lack of mechanical stimuli of the bones is the main culprit. The underlying mechanisms of the two phenomena on the molecular and cellular level are nevertheless identical. The medical community believes that detailed research enabled by long duration human spaceflight and the possibility of performing in vitro bone cell experiments aboard the International Space Station can shed some light on the origins of a disease responsible for 650,000 fractures each year in the European Union alone.



From left to right, low power scanning electron microscope image of a normal bone architecture in the third lumbar vertebra of a 30 year old woman vs osteoporotic architecture in the fourth lumbar vertebra of an 89 year old woman. The bone is heavily eroded in places by the action of osteoclasts and consists mainly of thin, fragile struts.
Credits: Alan Boyde, a.boyde@qmul.ac.uk

BONE LOSS IN MICROGRAVITY

The human body evolved within an environment of constant Earth gravity. The skeleton and the muscles serve as a powerful motion apparatus that enables us to stand upright and move against the power of gravity. Once gravity is eliminated, we can move effortlessly. Bones and muscles therefore start weakening as there is nothing forcing them to stay strong. Studies have revealed that astronauts lose approximately 1-2% of bone mass for every month they spend in space. Post-flight recovery of the lost mass can exceed twice the time of the flight itself.

Bone is an organic tissue that flexibly responds to external stimuli. During a period of increased exercise bone piles on mass, during decreased activity it weakens. It continuously rebuilds itself through resorption and formation, in a cyclic process known as remodeling. When resorption takes place, the bone calcium is excreted into the blood stream and then to the urine. Bone cells adapt to the variables of mechanical stress, and it is only this stress that makes them perform efficiently.

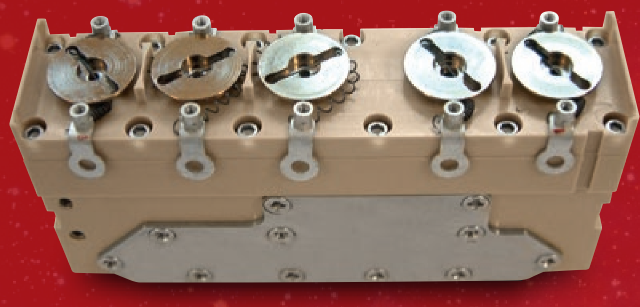
There are two types of cells responsible for this cycle - the osteoclasts and the osteoblasts. Osteoclasts secrete chemical substances that dissolve calcium and other minerals, degrading the bone. Small pits are created and then filled with osteoblasts that produce new bone material inside the pit by secreting calcium and proteins. The process of remodeling is fastest during puberty. At more advanced ages, bone loss compensation takes a significant amount of time.

In the 1970s, longer spaceflight missions began taking place thanks to the first space stations. At the same time, advancement in analytical technology helped researchers describe the bone loss process in greater detail. From the three Skylab missions of 29, 59, and 84 days, doctors learned how bone density loss is distributed throughout the body, proving that the most severe bone loss takes place in the heel while upper limbs remain almost unaffected.

This phenomenon was later confirmed and examined in greater detail by a study on 15 MIR cosmonauts, which proved that bone loss occurs first at the level of the lumbar spine and increases in the bones of the legs in the downward direction. Even after several months in space, the arms still remained unaffected. These studies also showed that the inner spongy trabecular bone is on average more affected than the outer hard cortical layer.

Several theories are trying to explain the reasons behind the uneven bone loss distribution during space flight. One of them assumes that whereas in terrestrial conditions legs are constantly bearing the biggest burden of our body weight, in microgravity astronauts predominantly use their hands and arms as the source of locomotion. Therefore legs become underused and the body doesn't feel the need to maintain their muscles and bones. On the other hand, arms experience a load increase and the body adapts accordingly. The same distribution of weakening applies also to muscles.

A second theory explains this phenomenon as being a consequence of the influence of weightlessness on the fluid distribution within the body. As there is no force pulling liquids towards the feet, fluids shift towards the head, causing redistribution of minerals within the body. The kidneys then react to the above average volume of liquid in the upper body by excreting it as urine. Along with urine, minerals are eliminated as well.

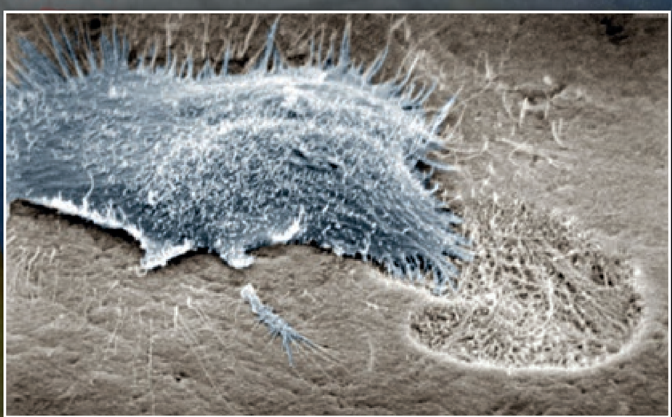


Kayser Italia's Stroma Experimental Unit, designed to study the bone marrow stromal cell differentiation and mesenchymal tissue reconstruction in microgravity through a fully automated protocol of BMSC cell activation, incubation and growth on a solid support, and fixation. The STROMA EU, which hosted five experiments since 2003, can host different supports allowing cultures such as BMSC, osteoclasts and umbilical vein endothelial cells.
Credits: Kayser Italia

MICROGRAVITY RESEARCH

Recent results have demonstrated that nutrition and sufficiently resistive exercise can noticeably improve astronauts' bone health. Research has shown that boosting vitamin K can help [(1)], as can use of the bisphosphonate family of osteoporosis drugs that interrupts the remodeling process by preventing mineral resorption. Current ISS study Pro K is investigating whether an increased ratio of consumption of potassium to animal protein can reduce bone mineral losses. The increased resistive capability of ISS' new aRED exercise device is also providing a boost for bone density since it doubled the resistive exercise capability of its predecessor [(2)].

JAXA's Medaka Osteoclast study, scheduled to launch aboard the SpaceX Dragon this year, will make use of the recently delivered aquatic habitat to study the fresh water fish medaka's bone response to microgravity. Such a study is only possible with the increased potential for transporting samples from ISS offered by Dragon, since the fish will be evaluated Earth-side for changes in gene expression.



Scanning electron micrograph showing osteoclast resorbing bone.
Credits: Prof. Tim Arnett, University College London

Another route to understanding microgravity's impact on bone is to examine cellular level mechanisms in *in vitro* studies. The primary targets for *in vitro* work are osteoclasts that are responsible for breaking down existing bone, osteoblasts that produce new bone, and bone marrow mesenchymal stem cells that produce both osteoblasts and osteoclasts. Current studies focus on whether microgravity causes these cells to respond differently on a molecular level than their Earth-bound relatives.

Although this may lend insight into space-based bone loss, there is an alternative school of thought that hypothesizes space is a better analog for cellular development than ground based cell cultures due to the fact that *in vivo* cells enjoy a buoyant growth environment in the body due to supporting bodily fluids that nearly mimic zero-gravity effects [(3)]. This buoyancy allows cells to grow in a three dimensional matrix. Lab based cultures, however, can only grow in two dimensions.

Much of the culture research in space has looked at equipment such as Kayser Italia's Stroma and Oclast Experimental Units (see box), supporting cell activation, incubation and three dimensional growth, and fixation in a self-servicing, fully automated environment.

(1) **Vico, L. and C. Alexandre. 2012. Zero Gravity: Bad to the Bones, Scientific American and ESA, Looking Up, 2008**

(2) **Smith, et al, 2012. Benefits for bone from resistance exercise and nutrition in long-duration spaceflight: Evidence from biochemistry and densitometry. JBMR, 27(9).**

(3) **Uhran, M.L. 2011. Positioning the International Space Station for the Utilization era. AIAA, Inc.**

RADIATION PROTECTION ON LONG DURATION SPACEFLIGHT

BY ROBERTO BATTISTON

Human exploration of space is among the most ambitious goals of mankind. This ambition, however, is not supported by our evolutionary DNA code.

Space, unfortunately, is a very hostile environment for man. Long duration missions to low Earth orbit (LEO) already require a technological marvel like the International Space Station (ISS). Exploration of the solar system beyond LEO poses much more difficult challenges, requiring the best of our technology and ingenuity to overcome them.

EARTH SHADOW PROTECTION

Protection from the effects of ionizing radiation, both short-term Solar Particle Events (SPE) and long-term Galactic Cosmic Rays (GCR), is a major issue. SPE are rare but very intense outbursts of ionizing particles from the Sun. Their energy is in the 1-100 MeV range but their flux can be so intense that they produce doses highly dangerous to astronaut health. GCR are a low but steady flux of high energy particles, peaking around 1 GeV, including all kinds of stable nuclei from protons to iron.

Exposure to ionizing radiation is seldom an issue on Earth: the effects of nuclear plant accidents or usage of nuclear weapons are the most extreme, but infrequent cases. On our planet we are well protected from the effect of cosmic radiation. The planet itself completely shields us over half of the solid angle, a phenomenon known as Earth shadow. The atmosphere acts as a massive shield equivalent to the thickness of 3.3 meters of aluminum. The Earth dipole magnetic field acts as a powerful deflector with 50 Tm bending power. The combined effect of Earth Shadow, atmosphere, and geomagnetic field contributes to almost eliminate the impact of GCR.

PROTECTION IN LEO

The situation changes substantially in LEO: the protection of the atmosphere is lost and the radiation dose absorbed by astronauts due to GCR increases nearly two orders of magnitude. But residence in LEO rarely exceeds six months, so by simply returning home, the absorbed dose can be maintained below professional exposure limits. The Apollo missions to the Moon lasted only about ten days and therefore did not present a health hazard from the point of view of total absorbed radiation. But an exploration mission, involving two to three years in space, represents a very significant step from the point of view of radiation protection: both the duration and the intensity of exposure to radiation are increased at the same time, reaching and sometimes exceeding current career limits.

Space radiation hitting cell DNA.
Credits: NASA

This issue has been known since the time of Werner von Braun. Several studies attempted during the last 40 years to find practical ways to protect astronauts from the sudden, very intense, low energy SPE and from the continuous flux of penetrating, high energy Galactic Cosmic Rays. Passive shielding works well for SPE, but is problematic for GCR: high energy hadrons can be shielded only using extremely heavy shields of a couple meters thickness, an approach used for ground based particle accelerators. Passive shields of a few centimeters thickness compatible with space usage have a tendency to increase the dose deposited by GCR due to secondary production.

The use of intense magnetic fields enveloping the spacecraft and deflecting charged cosmic radiation has been considered by various authors. This approach appears likely to be the most effective, although technologically challenging, active protection method. The power required to deflect most of the GCR requires magnetic fields on the order of magnitude of 1 Tesla extending over about 10 meters. Strong, large volume magnets in space, however, can only be based on superconductivity due to basic power and mass considerations.

ACTIVE MAGNETIC SHIELDING

Detailed analysis and accurate Monte Carlo simulations are required to identify realistic magnetic configurations that would optimize mass of the support structures needed to counter the large magnetic forces that are present within an active shield. Such a detailed analysis was started for the first time in 2011 in a ESA study [(1)] that will continue over the next three years within the frame of the recently approved FP7 Superconducting Radiation Space Shield (SR2S) project [(2)].

Earlier studies were based on the use of toroidal fields created by radially mounted coils. The ESA study considered alternative coil configurations based on an innovative *Double Helix* (DH) [(3)] design which is more promising from the point of view of the structural mass needed to counter the strong magnetic forces. The study shows that using different coil designs can significantly vary the weight/bending power with, for instance, up to a 30% reduction for a design based on DH coils and 4 Tesla meter (Tm) bending power.

The ESA study also yielded important results in understanding the interplay between active and passive shielding effects. Although intuitively, one might expect increased shielding mass to automatically reduce radiation, it turns out that is not the case. High energy particles produce secondaries which tend to increase the flux of charged particles. This phenomenon mandate the use of low mass coil materials and careful choice of structural materials to ensure attempts to protect against radiation are not achieving the opposite effect.

The study analyzes the merits of an active shield which could be built using existing state of the art technology. An active shield based on a 4 Tm Double Helix multicoil design around a spacecraft's habitable module would be able to reduce the GCR dose by nearly 40% with respect to the deep space dose, taking it below the current dose yearly limit of 50 rem/yr for Blood Forming Organs (BFO). This active design would have the advantage of effectively shielding astronauts from the lower energy SPE.

Magnetic shielding could offer a crew protection similar to that of Earth's magnetosphere.
Credits: NASA

Matroschka is an ESA-Roscosmos experiment co-developed by Kayser Italia. Named after Matryoshka nested dolls, the experiment uses a realistic human torso of polyurethane material and natural bones that simulates the densities of human tissues in order to establish the relation between radiation doses at the skin surface and at different locations inside a realistic human torso.
Credits: ESA

Future work within the FP7 SR2S program will deal with improved superconducting magnets able to reach higher field strengths, will study better shield materials and will provide detailed thermal and structural analyses. NASA has recently started similar work supported by the NASA Institute for Advanced Concepts (NIAC) and in close collaboration with the ESA and SR2S team.

There is consensus among experts that optimized combinations of passive and active shields, based on magnet technologies that are either available today or will be available within the next decade, should be able to reduce the absorbed radiation dose well below current limits.

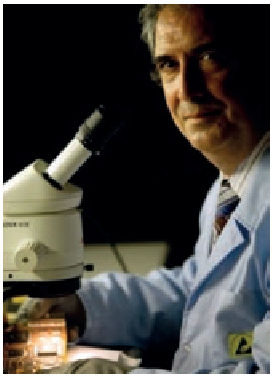
(1) R. Battiston *et al., An Active Radiation Screen Design Based on Superconductive Double-Helix Solendoids*, Proceedings of the 5th IAASS Conference *"A Safer Space for a Safer World"*, Versailles, France 17-19 October 2011 (ESA SP-699, January 2012); ARSSEM report http://arxiv.org/abs/1209.1907

(2) *Space Radiation Superconductive Shield (SR2S)*, approved under the call FP7-SPA-2012.2.2-02

(3) C.L. Goodzeit et al., The double-helix dipole a novel approach to accelerator magnet design, IEEE Trans. Appl. Supercon, 13, 2, 1365 – 1368, (2003); R. B. Meinke, Modulated double-helix quadrupole magnets, IEEE Trans. Appl. Supercon, 13, 2, 1369 – 1372, (2003)

Roberto Battiston is professor of physics at the University of Perugia and President of the INFN Committee on Astroparticle Physics. Deputy spokesperson of the AMS experiment on the ISS, he has coordinated the ESA Study for Active Radiation Shields for Space Exploration (ARRSEM Report) and currently coordinates the SR2S FP7 program aimed to improve the technology for superconductive radiation shields.

KAYSER ITALIA: THE COMPANY



Kayser Italia is a Small-Medium Enterprise (SME), a private independent aerospace system engineering company owned by Dr. Valfredo Zolesi's family. It was incorporated in 1986, and since 1995 it is 100% Italian property. The company is located in the countryside of Livorno, in the region of Tuscany, 20km south of the international airport of Pisa and 90km from Florence. In a modern building, the company has 5,000m^2 of property, organized into offices, meeting rooms, conference room, laboratories, a clean room, a manufacturing, inspection, and integration area, and an User Support Operation Center (USOC) to support the execution of experiments by astronauts onboard the International Space Station (ISS). The working area is surrounded by a property of 22,000m^2 of Mediterranean woodland.

From its beginning up to 2012, Kayser Italia has participated in more than 50 space missions with 80 payloads and experiments, all of them completed with full scientific, technical, economic, and programmatic success. The staff consists of 40 highly specialized engineers, with expertise in electronics, aeronautics, mechanics, thermodynamics, physics, computer science, optics, and molecular biology. Their design and manufacturing capabilities, joined with a deep engineering background, have allowed the company to participate both as prime contractor as well as sub-contractor for many European Space Agency (ESA) and Italian Space Agency (ASI) programs, especially in the area of life science (biology and human physiology).

The payloads developed by Kayser Italia have been flown on the Russian capsules Bion, Foton, Progress, and Soyuz, on the Space Shuttle, on the Japanese HTV, on the European ATV module, and of course on the ISS. In 2011 an incubator was flown with the Chinese Shenzhou 8 capsule. In 2012 the flight of an ESA Transport container is planned with SpaceX Dragon.

Kayser Italia is certified ISO 9001, and its personnel is qualified to manufacture and inspect electronic circuits and harness in accordance with ESA standards. The company supports grants and partnership programs with universities and research institutes and is actively involved in the promotion of the integration process between large and Small-Medium Enterprises working in space.

Looking forward to the next 25 years of successes.

Dr. Ing. Valfredo Zolesi
President
Kayser Italia