Sheba Medical Center

Tel Hashomer

Bio- Medical Research and Development Services

For Scientists and the Medical Industry

Bio-Medical R&D Service and Facilities

At the Sheba Medical Center

The Sheba Medical Center provides comprehensive R&D services in a unified environment from the very first stages and up to clinical trials. Our cutting-edge technologies, supported by world-renowned researchers, make us an ideal choice for your company.

Making a Difference in Treating Human Diseases

Bedside	Bench	Bedside
Clinical Problem	**Problem - Solving Team**	**Clinical application**
Clinical data	Tissue bank and biological samples	Final prototype
Pathophysiology	Genomics and bio-informatics	Clinical trials
Diseases	Transgenic animal models	Product
Family traits	Stem cell	
	Medical imaging tools	
	Health IT and informatics	
	Comparison medical research	
	Preclinical studies - animal models	
	Animal surgery rooms	
	Clinical database	

Tel Hashomer Medical Research,

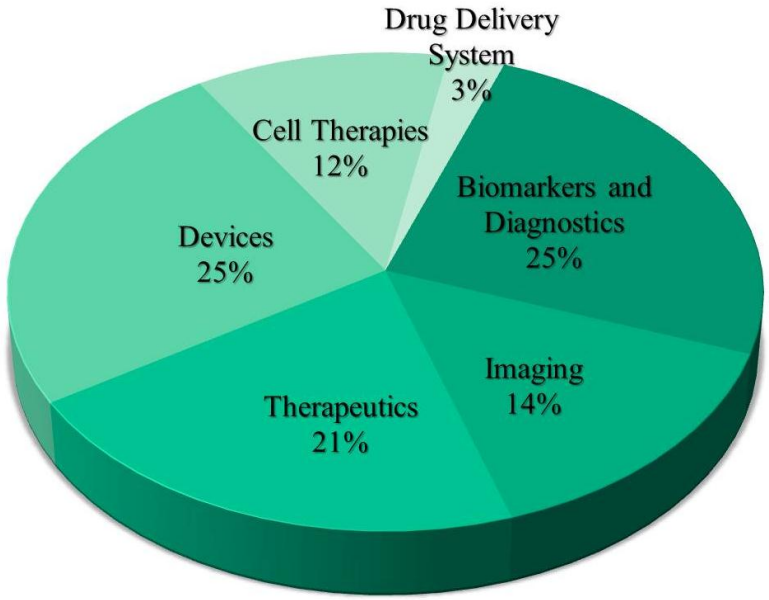
Infrastructure and Services Ltd.

Accelerating Bio-Medical Innovation

The Sheba Medical Center, Israel's largest hospital has made a commitment to clinical excellence, based on a strong research and development foundation, by investing in professional human resources, infrastructure and facilities. Sheba provides its staff with a working environment that stimulates research and innovation of major medical needs. Sheba's excellence is highly acknowledged in Israel and around the globe.

Tel Hashomer Medical Research, Infrastructure and Services Ltd. Promotes the transfer of technologies, innovation and professional know-how generated by hospital employees to the biomedical industry. All resources generated by the company are used to support research and education at the hospital

Our IP portfolio spans diverse medical fields, including therapeutics, diagnostic tools, imaging modalities, drug delivery systems and medical devices.



Medical Technologies - Opportunities for both Investors and the Industry

- Our medical innovations are developed by physicians and aimed at answering their most urgent medical needs.
- We have built dedicated infrastructures including a med-tech hub and a biocluster community with key opinion leaders.
- Our research and development facilities – leading from an idea to product provides a one-stop-shop
- We provide a wide range of licensing options on fair and reasonable terms.
- We have signed research collaborations with several research institutes and major industrial companies.
- We are the clinical arm of the Israeli medical industry.

Ventor – Aortic Valve

BI Biological Industries *Culture of Excellence*

TECHSO 3D Medical Simulations

cCAM Biotherapeutics

ACCUTOME® "Where The Difference Is Visible"

RADLogics™ Enhancing Radiologists' Success

Gamidor Diagnostics

Sanoculis Novel Glaucoma Treatment

Eximore

Spring BioMed Ltd.

orgenesis™ Cell Therapy to Treat Diabetes

The Animal Research and Service Center

Dr. David Castel

The Animal Research and Service Center at the Sheba Medical Center provides Specific Pathogen Free (SPF) laboratory animal care.

The animal facilities are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

- Our mission is to become the pioneer in laboratory animal care, driving research innovations from bench to bedside for all biomedical applications.

- We are committed to supplying quality laboratory animals; husband them in a modern and well-maintained environment, and ensuring the highest levels of welfare and ethical standards of animal care.

- We are committed to the highest standard of veterinary services, principal investigators, study directors and technicians, to assist with all medical research and development procedures.

- We lead small and large animal models contract research for biomedical product development, including animal models for drug discovery and efficacy, diagnostic and disease management and medical device development in numerous medical fields.

- Our state-of-the-art facilities support development studies in various animal models, including mice, rats, rabbits, zebra-fish, pigs, goats and more for various medical needs.

- The **Animal Research and Service Center** offers well-equipped research laboratories with a state-of-the-art surgical center in GLP-compliant research facilities for numerous medical needs, with all the support equipment required of advanced operating rooms.

- We provide on-site support services, including histopathology laboratory, animal imaging and molecular imaging services, a pressure-volume loop machine, an MRI for small and large animals, X-ray imaging and more.

- We provide biological radiation services for in-vitro and animal studies, using the advanced Kimtron's Orthovoltage comprehensive system. The service is suitable for drug development with ionizing radiation, normal tissue radioprotection, tumor cell radiosensitization, conditioning prior to bone-marrow transplantation, and development / exposure / calibration of dosimetric equipment. These services are integrated within the Radiobiology lab within the Radiotherapy Institute at the Sheba Medical Center.

- Our clients include hospitals, universities, start-up companies, industry leaders

and businesses.

The **Animal Research and Service Center** provides high quality animal care and veterinary services, and advises and educates researchers, staff and students on animal experimentation issues, while promoting best practices for the responsible use of animals. These actions result in quality science hand-in-hand with humane and responsible animal welfare.

The Pathology Research Institute

Prof. Iris Barshack – Head

The **Pathology Research Institute at the Sheba Medical Center** is the largest pathology department in Israel, and the leader in teaching clinical and research needs.

- Our mission is to improve the diagnosis, treatment and basic understanding of human disease by clinical service, education and research programs.
- We are committed to top care, providing pathology diagnostic services in vast medical domains.
- We are committed to advancing basic science, transnational and clinical research in the fields of pathology and related fields.
- We are committed to teach medical and graduate students, residents and fellows, and foster the development of leaders in pathology and related fields.
- We collaborate with hospitals, universities and with industry leaders to understand - and to ultimately arrest and reverse - disease processes of medical and social significance.

Our Core Technologies

- Immunohistochemistry and in-situ hybridization.
- Fish and CGH.
- Electron Microscopy.
- Tissue Microarray.
- PCR on tissue specimen.
- Cytology.
- Molecular Pathology.
- Personalized medicine.

Our research Programs

- microRNA in different tumors
- FISH in brain tumors.
- FISH in lymphomas.
- FISH in bladder cancer.
- Immunohistochemical and in-situ hybridization diagnostic and prognostic markers in effusions of ovarian carcinomas.
- Immunohistochemical markers for differential diagnosis of renal cell carcinoma.
- Immunohistochemical markers for diagnosis and prognosis of tumors of the gastrointestinal tract.

The pathology Institute occupies over 1000 m^2, with archives handling over 60,000 pathological and cytological specimens per year. The team of 50 employees includes 12 pathology specialists with specific fellowships in the following fields: hematopathology, neuropathology, pulmonary pathology, breast pathology, gynecopathology, uropathology, gastrointestinal pathology, soft tissue pathology, dermatopathology, cytopathology, nephropathology, oral pathology, E.N.T. pathology and more.

Tissue Repositories for an Advanced Biomedical Research Center

Prof. Iris Barshack, Dr. Amir Onn, Dr. Yehudit Cohen

The **Tissue Repositories for an Advanced Biomedical Research Center** aims to facilitate biomedical research, providing the highest quality and well annotated biological biospecimens. We provide tools for the growing demands of the bio-medical needs to accelerate research and medical product development through clinical resources.

- We provide the highest quality, sector-leading, cost-effective tissue banking services and facilities to the public and private sectors, leading best practices, adopting the most appropriate processes and applying ethical approaches to long-term storage of human tissue.
- Our Tissue Repositories**,** activities and services include collecting and banking freshly-frozen tissue specimens from excess surgical material and from autopsies, providing fresh tissue specimens for viable cell studies, processing and banking blood components, maintaining a tissue database with links to clinico-pathological data, performing histological staining and pathological reviews, as well as coordinating patient consent and assuring regulatory compliance.
- The Tissue Repositories adds value through experience, efficiency, standardization, accountability, protection of patient confidentially, and timely completion of research. An oversight committee serves to guide policies, prioritize resources, and review service requests to ensure fair usage.

The Tissue Repositories for Advanced Biomedical Research services includes:

- Banked frozen and fresh tissue specimens: we provide frozen and fresh tissue specimens, along with a pathologist-reviewed H&E-stained frozen section for quality assurance, and basic clinicopathological information distilled from the Pathology report.
- Formalin-fixed paraffin-embedded tissue: Investigators are provided with paraffin-embedded tissue (typically as thick sections), either from the Pathology Department archive or from the separate Tissue Bank research archive, along with a pathologist-reviewed H&E-stained paraffin section for quality assurance, and basic clinicopathological information distilled from the pathology report.
- Banked frozen serum/plasma and leukocyte DNA specimen: Investigators are provided banked frozen serum or plasma specimen and leuckocyte DNA, with basic clinicopathological information distilled from the Pathology report.
- H&E-stained frozen and paraffin section: Investigators are provided an H&E-stained slide of sectioned frozen tissue specimen.
- Unstained frozen and paraffin section: Investigators are provided an unstained slide of sectioned frozen tissue specimen. Additional unstained slides from the same specimen are available at a reduced price.

The Tissue Repositories for an Advanced Biomedical Research Center with its multi-disciplinary team provides tools for researchers at universities, hospitals and industry to accelerate and support the development of novel medications and diagnostic tools.

Biomedical Imaging Research Institute

Computational Imaging Laboratory – CILAB

Prof. Eli Konen, Dr. Arnaldo Mayer

At the heart of Israel's most advanced Radiology Department, top medical expertise meets state-of-the-art image and signal processing. Enjoying an unlimited access to radiological data and clinical expertise, the CILAB is in a privileged position to foster the development of advanced software and devices that solve challenging medical problems.

The CILAB is involved in several joint research projects with Academia and Industry.

It is a one-stop-shop for medical device companies, providing support from the basic idea to the validated prototype:

- State-of-the-art algorithm development for medical image & signal processing
- Advanced machine-learning methods, applied to large medical data bases (text, voxels, physiological signals)
- User interface development
- Embedded implementations
- Feasibility studies and prototyping
- Clinical studies and validation of devices at the Sheba Medical Center
- R&D under chief scientist grants

The Biomedical Imaging Research Lab is actively engaged in several areas of translational research with emphasis on scientific analysis and visualization of multi-modal images and on image-guided, computer-assisted, minimally-invasive clinical procedures.

www.cilab.org.il

Cancer and Genome Research Center

Prof Gidi Rechavi, Prof. Ninette Amariglio,

The Cancer and Genome Research Center is a state-of-the-art genomics facility dedicated to providing the latest genomic research and development tools for scientists and medical industry, to facilitate high-impact genomic-based cancer product developments .

- We provide access to cutting-edge technologies and provide the services, expertise, and scientific support necessary for utilizing genomic tools.
- We provide guidance with experimental design and data analysis combined with clinical data and data archiving.
- Microarray services using fully equipped microarray production clean room facility and can produce microarrays of cDNAs and oligonucleotides material
- Microarray Processing services for a variety of microarray platforms utilizing Affymetrix, Agilent, Illumina, Nimblgen, and other commercial and custom arrays.
- High-throughput Sequencing using Illumina Genome Analyzer for whole-genome and candidate region resequencing, transcriptome analysis, small RNA discovery, methylation profiling, and protein-nucleic acid interaction analysis at the genome-wide scale.
- Access to the bioinformatics resources is provided through our web-based interface for depositing, retrieving or analyzing data, publishing data sets, and collaborative sharing of the data.

Doctors and scientists at the Sheba Cancer research Center are engaged in state-of-the-art clinical and pre-clinical research that brings to cancer patients the most advanced diagnostic and treatment modalities. In addition to academic teaching and training, Sheba's doctors collaborate with leading international research groups as well as major pharmaceutical and biotech companies. Numerous clinical studies are conducted for developing new anti-cancer drugs. Advanced technologies such as Gene-sequencing, Microarrays, Bioinformatics, Molecular Cytogenetics, Stem Cells and others, are employed and constantly improved. Several applied R&D programs are at various stages of development of new treatment modalities.

The Advanced Technology Center

Prof. Arie Orenstein, Dr. Yael Mardor

The Advanced Technology Center specializes in interdisciplinary translational medical research in the fields of biomedical photonics, drug delivery into the brain and brain tumors and brain MRI.

We develop/apply cutting-edge photonic/MRI technologies and provide the services, expertise, data analysis and scientific support necessary for utilizing these technologies in animals/humans

Our unique expertise and novel inventions in MRI of primary/metastatic brain tumors post various conventional/novel treatments have turned us into a referral center in Israel with numerous international collaborations. Our unique methodologies enable high resolution (1 mm^3) and complete separation between tumor/treatment-effects enabling accurate assessment of response/progression for various treatments by easy-to-interpret color maps.

Brain, brain tumors and MRI

- Vast experience in MRI of phantoms, small/large animals, clinical studies
- Mice/rats with intracranial tumor models
- Drug delivery into the brain/tumor (including convection-enhanced drug delivery for molecules/nano-carriers, various methods for BBB disruption, real-time MRI monitoring of BBB disruption, drug distribution, MRI depiction of early/late toxicity and more)
- Unique MRI methods for differentiating tumor from treatment effects (such as radiation necrosis)
- Unique MRI methods for depiction of subtle BBB disruption (for example in stroke or following various treatments)

Biomedical Photonics laboratory services

- Tissue cultures
- Animal models for human diseases
- Laboratory experiments
- Conducting human clinical trials
- alpha/beta site
- Consulting
- Equipment: lasers, MRI, Ultrasound, cameras, microscopes, optical imaging equipment, spectrometers, etc.

The Advanced Technology Center occupies over 2000 m^2 with biological, optical, computers and MRI-based laboratories. The interdisciplinary team includes biologists, chemists and physicists with vast experience in applied medical sciences and a wide range

of collaborations within Sheba Medical Center and with other hospitals, academic institutions and pharma/medical device industries in Israel and abroad.

Phase I Unit - Therapeutics, Diagnostic, Medical Devices and Data Mining

Dr. Raanan Berger Dr. Talia Golan

Our Commitment

- To perform clinical trials to the highest scientific and ethical standards.
- To inspire hope in our patients, and contribute to their health and wellbeing by providing them with the best possible care.
- To perform outstanding scientific research, basic, translational and clinical.
- To facilitate the transfer of scientific knowledge into clinical practice, pushing forward the boundaries of medicine.
- To promote scientific cooperation among national and international cancer research centers
- International Phase I Unit

Sheba Medical Center has successfully developed the first oncology dedicated Phase I unit in Israel. It is currently the best place in Israel to further develop early phase clinical trials.

The Early Phase Trial Unit has an excellent track record of accruals and performance which has already attracted international academic and industry attention.

Through the Early Phase Trial Unit, we are positioned to bring additional pharmaceutical and biotech companies to Sheba for innovative drug development programs.

Early-Phase Research Activity

Merck Sharp & Dohme selected Sheba's Unit to be part of its global network of 19 leading cancer centers for early phase R&D.

- Sheba MC has been chosen to participate in the innovative WINTHER trial consortium to select rational therapeutics based on the analysis of matched tumor and normal biopsies in 200 subjects with advanced Solid Tumors together with Gustave Roussy (France), MD Anderson Cancer Center (USA) and Val D'Hebron Institute (Spain).
- We provide robust Standard Operating Procedures (SOP) in place since 2011.
- We provide special fast IRB approval process for approval of oncology Phase I trials which is highly attractive to industry sponsors.
- Recruitment rate is greater than sponsor targets
- Sheba is a referring center for patients who are candidates for oncology Phase I clinical trials.

The Danek Gertner Institute of Human Genetics

Prof. Alon Prass

The Danek Gertner Institute of Human Genetics comprises two major arms that operate in synergy. The genetic medical clinic, that provides specialist consultancy and laboratory services, and the research laboratory. Our primary goal is to provide the patient with superior, cutting edge medical care by coupling the clinical activities with the advanced scientific research and development.

The Molecular Diagnosis Laboratory collaborates with the Israeli Genetic National Database on an ongoing basis and performs more than 70,000, diverse, diagnostic tests a year, to great success:

- Cytogenetic testing - Providing prenatal and patient chromosome analysis (classical G banding).
- Chromosomal Micro Array - Micro Array for the detection of small chromosomal aberrations in pre and post natal settings (CMA).
- Biochemical markers - Pregnancies at-risk for chromosomal Aneuploidy, mainly Trisomy 21 are detected through maternal serum biochemical marker tests in both the first and second trimesters of pregnancy.
- A broad spectrum of biochemical and molecular testing - These tests are carried out at both the carrier detection and prenatal diagnosis levels for metabolic diseases, such as Tay-Sachs, Fragile -X Syndrome, Bloom Syndrome and more.
- Molecular cytogenetic facility - We offer fluorescent in situ hybridization (FISH) for rapid chromosomal analysis (within 24 hours) and Quantitative Fluorescent PCR (QF-PCR) in a wide array of tissues: Amniocytes, placental villi, fibroblasts, fetal tissues etc.
- Preimplantation genetic disorder (PGD) - This technology enables identification of non-affected embryos, before implantation with IVF technology.
- The Noninvasive Prenatal Diagnosis Laboratory:
  - Identification of fetal trophoblast cells in maternal peripheral blood.
  - Fetal sex detection in maternal plasma cell-free DNA.
  - Fetal RhD diagnosis in maternal plasma cell-free DNA.
- New Generation Sequencing - Numerous panels of common known mutations for chosen diseases are being analyzed using techniques of NGS.

The Danek Gertner Institute of Human Genetics is affiliated with Tel Aviv University's Sackler School of Medicine. Hence, the senior staff consists of multidisciplinary, highly experienced, scientists and doctors who give 3,000 genetic consultations annually in various fields:

- Gene testing for diseases.
- Genetic amniotic fluid analysis.
- Genetic clinic for the elderly.
- Testing and consultations regarding inherited diseases, birth defects and cognitive deficits such as Autism, Intellectual disability and specific developmental disorders.

- Prenatal genetic counseling for embryo defects detection, repeat abortions and infertility.
- Counseling for families with specific history of cancer.
- Preimplantation genetic diagnosis (PGD) consultant.

All the relevant departments at the Sheba Medical Center enjoy in-house access to the consultancy services of The Danek Gertner Institute of Human Genetics.

Infectious Diseases Research Laboratory

Prof. Galia Rahav and Dr . Ohad Gal-Mor

The Sheba Medical Center's Infectious Diseases Unit is the largest of its kind in Israel. In addition to the Infectious Diseases Research Laboratory, the unit provides diagnosis, vaccinations and treatment services in the fields of HIV and sexually transmitted diseases, Infections Control, Tropical diseases and travelers' clinic and a Pediatric Infections unit.

The Infectious Diseases Research Laboratory provides the most advanced molecular microbiology research services tailored to client needs. Our lab is equipped with state-of-the-art biosafety level 2+ facilities that enable us to encompass comprehensive infectious diseases research. Sheba's Medical Center infrastructures allow us in-house utilization of advanced analysis methods such as Microarray laboratory (for Affymetrix Arrays analysis) and NGS (next-generation sequencing) platforms including the Illumina Miseq and Hiseq platforms. The new institutional SPF animal facility allows utilization of diverse animal models.

The Sheba Medical Center holds a unique collection of hundreds of clinical (human) and veterinary bacterial isolates of many pathogens, with extremely high clinical value for drug development and target diagnostic tools. Our pathogen repository is available for research and development collaboration and services for various analyses such as:

1. Analysis of antimicrobial activity of biological and synthetic compounds.
2. Antibiotic resistance and sensitivity profiling.
3. Bacteria identification and characterization.
4. Determination of genetic relatedness (clonality) between bacterial isolates.
5. Virulence and pathogenicity characterization using diverse model systems.
6. Biofilm formation and bacterial attachment to organic and inorganic surfaces.

The Center of Advanced Technologies in Rehabilitation

Dr. Itzhak Siev-Ner, Dr. Gabi Zeilig, Dr. Meir Plotnik

The Center of Advanced Technologies in Rehabilitation holds the most progressive and comprehensive set up of clinical and research laboratories worldwide. In these laboratories we conduct basic, clinical and applicable research. **In particular our facilities include:**

- Gait and motor control laboratories with motion caption systems that allow sampling human movement with high spatio-temporal resolution. Thus we can reconstruct and analyze the kinematics of each motor action performed by the limbs or any other body part.
- Special treadmills that are equipped with dense force sensitive sensors, thus the pressure application during stepping can be evaluated. Special carpet and force plates embedded in the laboratory's floor, allow capturing the pressure application during stepping also during over ground walking.
- Split belt treadmills - allowing the application of different speeds for each leg, and thus study and train inter limb coordination.
- Wearable sensors for studying motor functions while the subjects are conducting their daily life activities within their home environments.
- Virtual reality laboratories are the most advance in the world (see figure). We are able to install different virtual environments, to use avatar technologies and to provide real time feedback on the subject being studied/ trained so he/she trainee can modify behavior. The subject's performance is also fed into the operating system for modifying the stimulation regime.
- Robotic systems – In the STEP institute of the rehabilitation hospital, there are several advanced robotic systems including the Lokomat - Robot-assisted Walking Therapy, which interface with human performance. In the motor level the interaction is whole body interaction for some devices, while in robotic devices the interaction is with the upper limbs or lower limbs.
- Technologies allowing tele-interaction between the subject and the researcher/therapist while the subject conducting a clinical/ research protocol at home .

Being the largest hospital in Israel, we have ready access to different patient populations (e.g., neurological, psychiatric, diabetes, orthopedic) and have ongoing collaborations with the clinical leaders in many medical disciplines.

<u>Research topics related to HEALTH, neuroscience and life sciences</u>

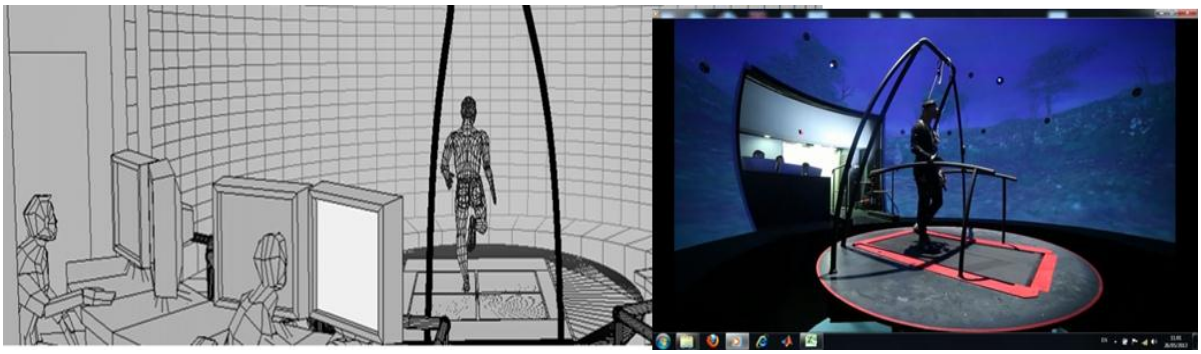
- Motor learning; Sensory- motor - cognitive integration in gait and posture.
- Pathophysiology of diseases of the nervous system .
- Mental, psychological and psychiatric interactions with motor performance.

Research topics related to Information and Communication Technologies (ICT) including Physics, Computing and Engineering

- Complexity in physiological networks – for short and long term physiological processes, based on signal processing data obtained from physiological sensors.
- Development of miniaturized wearable devices for diagnosis and treatment .
- Technologically based diagnostic, treatment, rehabilitation and tele-rehabilitation tools.

The center of advanced technologies services:

- Conducting clinical trials
- Renting laboratory time
- Consulting



Schematic drawing of the Caren High end (left). While the subject is walking on a split belt treadmill, embedded on a moveable platform (6D of freedom), a virtual environment (e.g., street scene – right) is projected by overlapping projectors that provide 360˚ cover of the scene and, together with auditory surround system enables high level of immersion.