

**PHASE I UNIT AND CLINICAL RESEARCH DEPARTMENT  
DEPARTMENT OF ONCOLOGY  
RIGSHOSPITALET  
COPENHAGEN, DENMARK**

# Rigshospitalet

Rigshospitalet is a highly specialized hospital, which has tasks within patient treatment, research and development, and training. Rigshospitalet has national and regional responsibilities within all medical specialties apart from dermatology, occupational medicine and child psychiatry. Rigshospitalet is part of The Capital Region of Denmark - one of five administrative units in Denmark. The Region provides among others healthcare, mental care, regional development and research for 1,6 mio. people – approx. 30% of the Danish population. Next to Rigshospitalet is the Panum Institute with the Medical Faculty of Copenhagen University. This secures close cooperation on research and development. Rigshospitalet has about 1.100 beds and there are more than 60.000 admissions and 400.000 outpatient visits every year. About 7.400 individuals are employed at the hospital – without counting personnel who are paid by foundations. Rigshospitalet ([www.rigshospitalet.dk](http://www.rigshospitalet.dk) - in Danish) is the most highly specialised hospital in Denmark and all medical specialities are present.

The mission of the hospital is to be Denmark's leading hospital for patients needing highly specialized treatment and care. Rigshospitalet is the patients' hospital, a major centre for medical research, the staff engaged in the whole range of patient treatment, research, development, and training.

Carrying both national and regional responsibility within virtually the entire spectrum of medical specialties, Rigshospitalet plays a prominent role within the Copenhagen Hospital Cooperation as well as the Copenhagen University Hospital System.

Rigshospitalet's role as the most highly specialised hospital in Denmark has been even further enhanced in recent years by the decision that it should serve as the host institution for most of the capital's specialised departments.


Joint Commission International has accredited Rigshospitalet in 2002, 2005 and 2008.

## Organisation

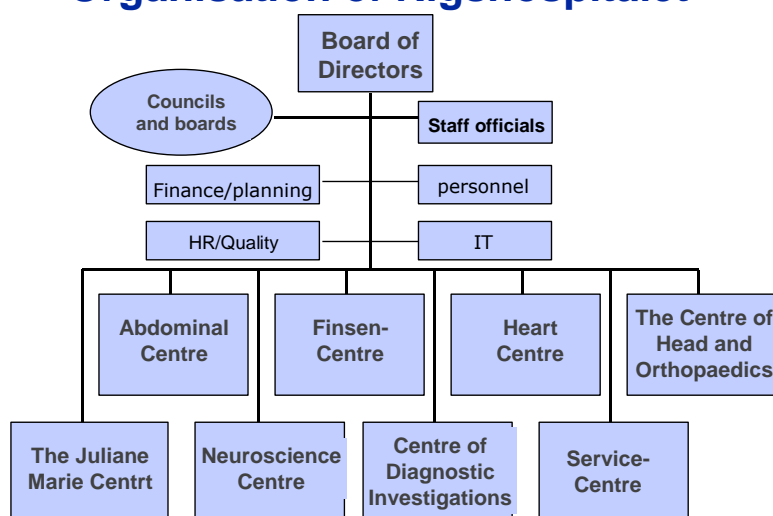
Rigshospitalet's management structure is a triumvirate, with a Chief Executive Officer, a Nursing Director, and a Medical Director, served by four administrative departments

- finance and planning
- personnel and human resource development
- quality improvement and
- IT.

The hospital is divided into six treatment centres and two service centres each centre with independent administrative and financial responsibility.

 Rigshospitalet

## Organisation of Rigshospitalet



Rigshospitalets organisations-diagram m3j 2001 (lg)

**The Abdominal Centre**

Medical Endocrinology  
Surgical Gastroenterology and Organ Transplantation  
Medical Gastroenterology  
Hepatology  
Nephrology  
Vascular Surgery  
Urology  
Anaesthesiology  
Intensive Multidisciplinary Care

**The Juliane Marie Centre**

Fertility, Clinical Genetics, Andrology  
Fetal diagnosis and therapy  
Gynaecology  
Haemophilia and Cystic Fibrosis  
Neonatology  
Obstetrics  
Paediatrics  
Paediatric Surgery  
Psychology, Play Therapy and Social Work  
Team for Sexually Abused Children  
Centre for Victims of Sexual Assault  
Ultrasound Diagnostics  
Anaesthesiology  
Paediatric Intensive Care

**The Centre of Head and Orthopaedics**

Breast Surgery & Surgical Endocrinology  
Trauma Centre  
Mobile Intensive Care Unit and Major Incident  
Command Centre  
Medical and surgical Orthopaedics  
Physio- and Occupational Therapy  
Plastic Surgery and Treatment of Burns  
Ophthalmology  
Oral and Maxillofacial Surgery  
Oto-rhino-laryngology  
Anaesthesiology

**The Service Centre**

Patient hotel, Conference facilities  
Catering, Staff restaurant, Café  
Internal Call Centre  
Technical Construction and Maintenance  
Purchase, Warehousing, Linen service  
Transport, internal post service, waste disposal  
Contracts for outsourced services

**The Neuroscience Centre**

Neurobiology, Neurology  
Clinical Neurophysiology  
Neurosurgery  
Multidisciplinary Pain Centre  
Spinal Cord Injury  
Psychiatry  
Crisis and Disaster Psychology  
Clinical Sexology  
Respiratory Centre East  
Neuroanaesthesiology  
Intensive Care

**The Finsen Centre**

Allergology  
General Medicine  
Haematology  
Infectious Diseases  
Oncology: Experimental, medical and radiation  
Medical Rheumatology

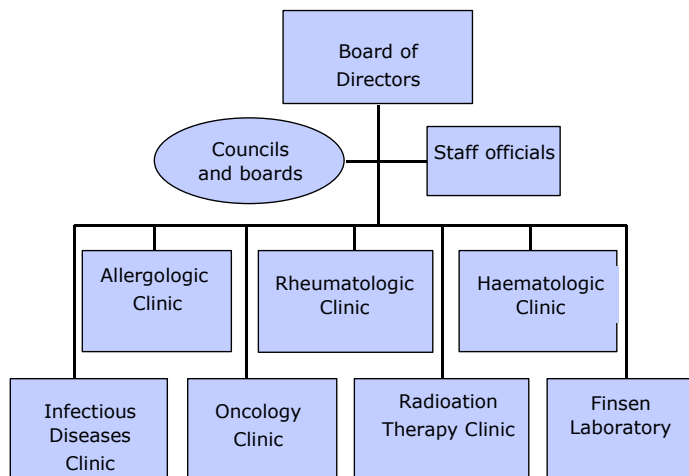
**The Heart Centre**

Cardiology  
Cardiothoracic Surgery  
Heart and Lung Transplantation  
Aviation Medicine  
Anaesthesiology  
Intensive Care Unit

**The Centre of Diagnostic Investigations**

Clinical Biochemistry  
Biomedical Engineering  
Blood Bank  
Laboratory of Gene Therapy  
Clinical Microbiology  
Clinical Pathology  
Clinical Pharmacology  
Clinical Physiology and Nuclear Medicine  
Radiochemistry and Radiopharmacy  
Radiology, PET-scans  
Tissue Typing Laboratory  
Bartholin Institute  
Copenhagen Trial Unit (CTU)

## Organisation of Finsen Centre



Rigshospitalets organisations-diagram maj 2001 (fg)

The Finsen Centre is one of eight centres at Rigshospitalet. Department of Oncology and Radiotherapy is part of the Finsen Centre.

All kinds of malignant diseases are treated at the department except leukaemia's and lymphomas.

The department have 64 beds + 4 beds for more complex experimental treatment.

The department delivered 18.000 in-patient days in 2008

43.000 patients were seen in the outpatient clinic in 2008

70.000 fractions of radiotherapy are administered every year.

Department of Oncology and Radiotherapy is a centre of excellence, which maintains an extensive network and fulfils a coordinating function within the field of oncology in the eastern part of Denmark.

The department operates in three key areas:

### *1. Clinical Research:*

Research activity of the department includes:

- Clinical trials of new therapies in phase I-IV
- Quality of life research
- Studies on long term effect of chemotherapy and radiotherapy

A comprehensive team for carrying out clinical oncological research have been established during recent years, including datamanagement and research nurses.

### *2. Scientific Research :*

#### **The Finsen Laboratory ([www.finsenlab.dk](http://www.finsenlab.dk))**

The research at the Finsen Laboratory is focused on proteolytic mechanisms in cancer invasion and metastasis. Several of the molecules involved in matrix degradation are revealed to be strong prognostic markers in various types of

cancer and the Department of Oncology is involved in these studies. The Finsen Laboratory is situated in the Biotech Research and Innovation Centre, close to the hospital ([www.bric.ku.dk](http://www.bric.ku.dk))

**The Department of Radiation Biology** ([www.radiationbiology.dk](http://www.radiationbiology.dk))

is a cancer research laboratory within the Oncology Clinic at the Finsen Centre, and part of The Copenhagen Cell Biology and Cancer Research network (The CCC Network Project) within the Faculty of Medicine, University of Copenhagen, ([www.ku.dk](http://www.ku.dk)). The general intend of the laboratory is to study molecular and phenotypic features of Lung Cancer and Brain Tumors.

Above all, growth factor receptor studies are of interest. The primary aim is to generate more insight into the influence of these growth factors on the malignant phenotype of cancer cells, and the secondary aim to extend that knowledge to patient material in terms of testing possible new diagnostic and prognostic tools, as well as suggesting new translational treatment modalities viz. targeting therapy and inhibition of signal transduction.

**PET and NMR functional imaging**

(<http://www.rigshospitalet.dk/menu/AFDELINGER/Diagnostisk+center/Klinisk+Fysiologisk+og+Nuklearmedicinsk+Klinik/In+English/>)

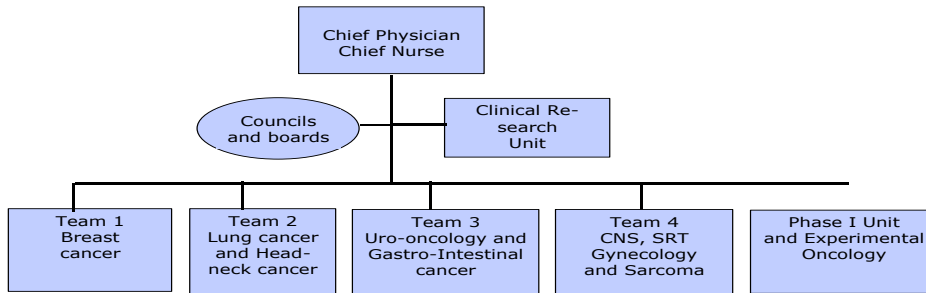
There is a close collaboration with the PET and Cyclotron Unit at Rigshospitalet. This unit is very well equipped with one THERASCAN 3128 PET scanner, one GE wholebody Discovery LS PET-CT scanner and four Siemens HiRez PET/CT scanner. The unit has a RDS Eclipse, CTI cyclotron, and automated production facilities. Collaboration includes research in the area of brain-, breast-, lung-, ovarian- and testis cancer together with unknown primary tumors.

In addition we have access to MRI (1.5 and 3 tesla), 5 64-slice Toshiba and one 320 slice Toshiba CT and dynamic CT, ultrasound Doppler with colour contrast enhancement and interventional diagnostic radiology. A small group of senior radiologists are dedicated to the clinical studies within the department and we have regular meeting concerning quality and coordination

*3. Teaching*

The department has a major commitment to clinical and post-graduate teaching in terms of research degrees and a MSc. course in Oncology. Currently 17 PhD students are affiliated with the Oncology and Radiotherapy Clinic.

## Organisation of Dept. Of Oncology



Rigshospitalets organisations-  
diagram majrch 2007

The Department of Oncology is divided into four teams. The head of the clinic is Professor, DMSc Han von der Maase, who is expert in renal cancer and bladder cancer.

Team 1 covers breast cancer.

In The Breast Cancer Team clinical trials are carried out within The Danish Breast Cancer Cooperative Group (DBCG). DBCG is in close cooperation with several international breast cancer cooperative groups, Thus, DBCG has taken up a significant position in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which has performed meta-analyses of all existing randomized studies concerning adjuvant treatment of breast cancer.

Furthermore, DBCG in 1994 took the initiative to form the Clinical Trials Committee (CTC) in the Scandinavian Breast Cancer Group (SBG), and DBCG is affiliated with the Breast International Group (BIG) established in 1996 with the purpose of coordinating studies between cooperative groups.

The team is managed by Professor, DMSc Henning Mouridsen, Consultant, DMSc Michael Andersson, Consultant, Ph.D., Bent Ejlersen, Consultant, Ph.D Anders Navrsted Pedersen and consultant Ulla Tange.

Team 2 covers lung cancer and head-and-neck cancer.

In lung cancer both national and Nordic clinical trials as well as industry sponsored trials are carried out. This includes translational research and clinical trials with pharmacodynamic analyses. The Lung Team had 250 new patients with NSCLC in 2006. The team are managed by, DMSc Jens Benn Sørensen, consultant, DMSc Helle Pappot, consultant, Ph.D. Seppo Langer, consultant. The Head and Neck Cancer Team is headed by DMSc Lena Specht and Ph.D. Claus Kristensen covers treatment and research in head and neck cancer, including new medical targeted therapies and advanced radiotherapy (IMRT). Clinical trials are carried out within the DAHANCA group and with international collaborators.

Team 3 covers gastrointestinal cancer and urological oncology.

In both upper and lower GI cancer industry and investigator sponsored trials are performed from phase I-III. Approximately 750 new patients with GI-cancer, including 200 with colorectal cancer, were referred to the clinic in 2006. The GI-group is managed by Ph.D. Lone Nørgaard, Ph.D. Lene Bæksgaard and DMSc Kell Østerlind, consultants, International collaborative studies of urogenital cancers are carried out in both bladder, testicular and prostate cancer as well as industry sponsored trials. Development of an array platform for diagnosis of unknown primary tumors is performed in this team. Professor, DMSc Mikael Roerth, consultant, DMSc

Phase I unit and Clinical Research Unit, Rigshospitalet, July 2009

Gedske Daugaard and consultant, Ph.D. Peter Meidahl Petersen are running this team.

Team 4 covers gynecological cancers, sarcoma and primary central nervous system tumors.

In gynecological cancers clinical trials are performed along with advanced radiotherapy, including brachytherapy, within national and Nordic trial groups. The GYN-group is managed by DMSc Henrik Roed and Ph.D. Mansoor Mirza, consultants. Trials of primary central nervous system tumors are performed in collaboration with EORTC. This disease group are managed by DMSc Hans Skovgaard Poulsen. He is also chairing early clinical trials of VEGF, EGFR, integrins, and mTOR-inhibitors in malignant gliomas, including biomarker studies and animal tumor models.

Clinical trials:

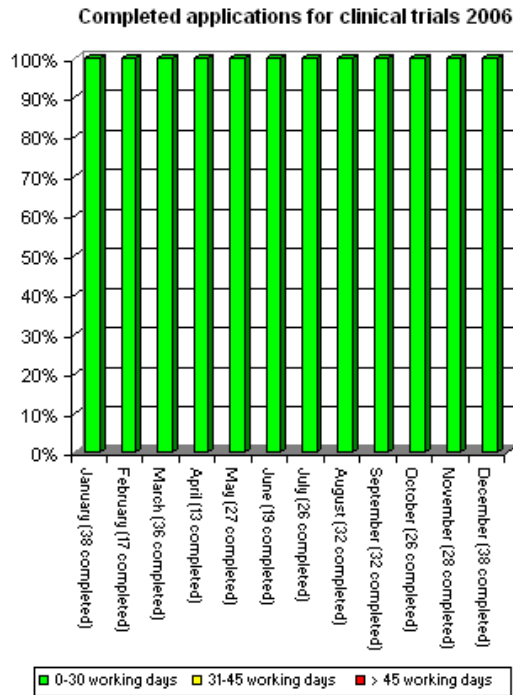
All clinical trials are managed according to GCP. It is the responsibility of the investigator to get approval from the institutional review board, which consists of the board of consultants.

In addition, the Danish Medicines Agency and the regional ethics committee must approve all trials. Since 1980 Denmark has had a system of research ethics committees with 5 [regional committees](#) and a national committee – “The Danish National Committee on Biomedical Research Ethics”.

The Danish Medicines Agency evaluates both the quality of the investigations and the safety of the patient during the clinical trial. The scientific ethical committee, which evaluates the ethical aspects of the investigation, must also be notified of clinical trials. In order for a trial to be approved, both the scientific ethical committee and the Danish Medicines Agency must give their approval (<http://www.dkma.dk>).

According to an agreement with the industry, the Danish Medicines Agency must handle applications for authorisation of clinical trials within 30 working days. The chart shows the case handling times for applications received by the Danish Medicines Agency during each month of 2006.

- The green bar of the chart represents the cases in which the time limit of 30 days is observed. The common European time limit for handling applications is 60 days, which corresponds to approximately 45 working days.
- The yellow bar represents the cases completed within 31-45 working days.
- The red bar represents the cases in which the maximum case handling time of 45 working days is exceeded.



It is seen from the Figure that the Danish Authorities have handling times well below the European limit of 60 days (compares to 45 working days).

Study applications are handled simultaneously in DKMA, the Institutional Review Board and ethical committees. The total handling time is therefore under 45 days.

## Phase I unit.

Drug development has been in focus at the Department of Oncology for more than 25 years. In recent years the technical demands of early clinical trials have increased. As a consequence, the department has opened a dedicated unit for experimental cancer therapy and phase I trials.

We offer complete project management and clinical trial management systems.

We are operating with ICH GCP to industry standards, including standard operating procedures (SOPs) covering all aspects of running clinical trials.

We comply with all current legal requirements and the needs of the EU Directive on Clinical Trials (Directive 2001/20/EC).

We are part of a network of leading scientists and oncologists, including collaboration with other phase I units in Europe and the US.

**Staff:** Ph.D. Ulrik Lassen and Ph.D. Morten Sørensen, consultants, are heading the experimental unit and responsible for most of the phase I-II early clinical trials. Every day two senior medical oncology consultants, specialized in early clinical trials and GCP, will perform their daily duty in the phase I unit. Six trained nurses together with two secretary are present at the unit. Junior doctors as well as ph.d. students are connected to the unit.

**Phase I and early phase II clinical trials:** Our unit is a semi-intensive care unit with facilities for close patient surveillance, including continuous cardiac monitoring. We have four fulltime beds with staff seven days a week and an outpatient clinic for therapy and follow-up. Our staff is experienced in developing, planning, implementing and running clinical trials, as well as processing the emerging data.

**Pharmacokinetics and pharmacodynamics:** Detailed pharmacokinetic (PK) and pharmacodynamic (PD) analyses are key components of phase I and II clinical trials. This includes biological and pharmacological studies on the new agent to ensure that it is acting by its proposed mechanism in patients and that a potentially active drug concentration can be achieved and maintained.

Our own staff of trained and GCP-examined research nurses obtain and handle blood samples for PK and PD in the laboratory facilities in the phase I unit. Tissue sampling and processing for further analysis including snap-freeze technique can be undertaken through our collaboration with the department of diagnostic radiology/pathology and the surgical departments. Extensive pharmacokinetic measures can be analysed at the neighbouring Department of clinical pharmacology and the University of Copenhagen (The Panum Institute).

**Immunological and clonogenic assays:** Through our network of local academic laboratories at Rigshospitalet, molecular biological/biochemical analyses can be undertaken, including:

- Immunohistochemistry and other immunological assays
- Micro-array gene analyses
- Chromosomal analyses
- Receptor expression and functional receptor analyses
- Proteomics

Our clinic has a close collaboration with in-house laboratories for experimental basic research in oncology.

## Track record

The Department of Oncology at the Finsen Center has have been running early clinical trial for more than 25 years. This includes early trials of gemcitabine and taxanes. We have experience with cytotoxic drugs, anti-angiogenic and EGFR agents, anti-hormonal agents, diagnostic agents, immunotoxins, therapeutic and imaging antibodies and drug resistance modifiers.

Since the opening of the phase I unit in the November 2004 we have performed >10 phase I trials in collaboration with several phase I unit form Europa and USA, including Royal Marsden in London, Dana-Farber Cancer Center in Boston, MD. Andersson in Texas and Fox Chase Cancer Center in Philadelphia. We have included > 50 patients annulally in these studies with major pharmaceutical companies, and have been co-authors of several phase I presentations at the ASCO meetings every year.

## Organisation

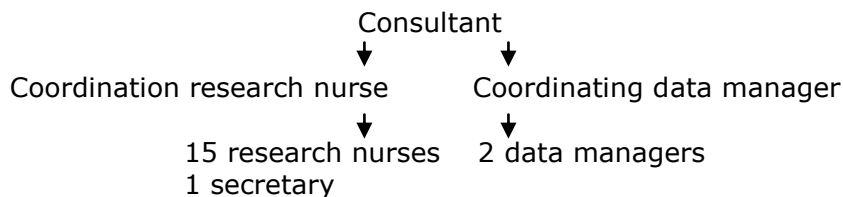
In January 2003 the Danish government launched a national programme for patients with advanced cancer. According to the programme, the physician in charge can ask for an independent assessment of the possibilities for further treatment from an expert panel consisting of two highly experienced Danish oncologists. Based on the advice from the panel the National Board of Health may subsequently approve public expense financed experimental treatment abroad or in dedicated units of experimental cancer therapy in Denmark.

As a consequence, a national coordinating board for experimental cancer therapy has been established in order to provide therapeutic options for patients to whom no standard therapy exists. Our phase I unit has been established with governmental co-financing within this programme. This ensures that patients from all over the country can be referred to clinical trials, including phase I trials with no costs incurred on the referring hospital.

The phase I unit is integrated in the clinical research department (CRU).

## **CLINICAL RESEARCH UNIT (CRU)**

### **Employees:**



### **Expertise in clinical trials:**

1. Preparation of protocols and case record forms
2. Approval from the local authorities
3. Identification of investigators
4. Trial monitoring
5. Data processing and development of databases
6. Clinical reports
7. Integrated clinical/statistical reports
8. Translation of protocols, patient information etc. into Danish
9. Electronic ordering of antineoplastic drugs and electronic access to all protocol related material

### **Preparation of protocols and case record forms**

Around 40-60 clinical studies are active at the department. Two thirds of the studies are performed in collaboration with the pharmaceutical industry or together with European research organisations (EORTC and MRC), one third of the studies are investigator initiated studies.

In case of investigator sponsored protocols CRU prepares:

- Protocol together with investigator
- Case report forms
- Signature log
- Correspondence with legal authorities
- Contracts with departments of pharmacy, radiology, clinical chemistry and clinical physiology
- Budget
- Information to the patient concerning the clinical study and informed consent
- Information concerning the medicine
- Contract with the GCP-unit in the Copenhagen area
- SAE and SUSAR reports
- Clinical report of the study

### **Approval from the local authorities**

CRU gets approval from:

- Ethical committee
- Danish Medicines Agency
- The Danish Data Protection Agency

The time frame for approvals from the ethical committee and from the Danish Medicines Agency are max.60 days.

### **Identification of investigators**

Specialists in all areas of oncology are employed at the Department of Oncology, Rigshospitalet.

## Trial monitoring

Half of the project nurses are examined monitors. CRU collaborates with the GCP unit for the Copenhagen area ([www.gcp-enhed.dk](http://www.gcp-enhed.dk))

## Data processing and development of databases

CRU's Data Management department offers consultancy services in connection with retrieval and processing of trial data.

Database programming is performed including data entry front-end on pc-based systems

- 32-bit database application programming
- Data entry front-end design and programming
- Generation of randomization lists
- Double data entry
- Discrepancy analysis of raw data
- "Clean File" declaration when the CRFs, the database, and the reference values are complete and logical according to the study protocol, general guidelines, and data entry instructions
- Full database source documentation
- Database query programming and export
- Digital data and file transmission (point to point or via internet)
- Presentation of data as tables or graphs on paper or overhead film

## International collaboration

Gedske Daugaard is head of one of the disease oriented groups in the EORTC-GU group. All important European centres treating urological cancer are present in this group.

Hans Skovgaard Poulsen, M.D., DMSc. is member of the EORTC Brain Tumor Group.

## For further information, please contact:

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