# Iranian Cancer Cluster

**Oncology Focused Research and Industry Cluster**

(Accelerate the development of Novel Therapeutics and diagnostics)

**Entire Value Chain:**

1-Academic Centers

2-Clinical Centers

3-International pharms

4-Biobank

5-Service providers

**Focus on**

-Collaboration

-Network building

-Innovation

-Capital development

**Public/Private infrastructure to support innovation**

**-Imam Hospital Research Foundation**

**-Mazandaran Cancer Cluster**

- Cancer Registry

-Pathology / Digital pathology

-Cancer Innovation Park

-Cancer Cluster Incubator

**-Institute for Cancer Research**

**Health Care Innovation: HUB**

+ capitalize science (e.g. Immuno-Oncology)

+global testbed for cancer [Precision Medicine]

+unique innovation campus and state of the art incubator

## Strategic Area

| | | |
|---|---|---|
| A. Collaborative Networks Academic/Business | B. Innovation | C. Access to Capital |
| D. Clinical Trials Efficiency | E. Public Policy | F.Work Force Competence Development |

**Track record for Successful translationfrom Bench to Bedside**

Discovery →Preclinical →Phase I →Phase II →Phase III →Marker

Discovery → Preclinical Development → Clinical → Approval →Sales

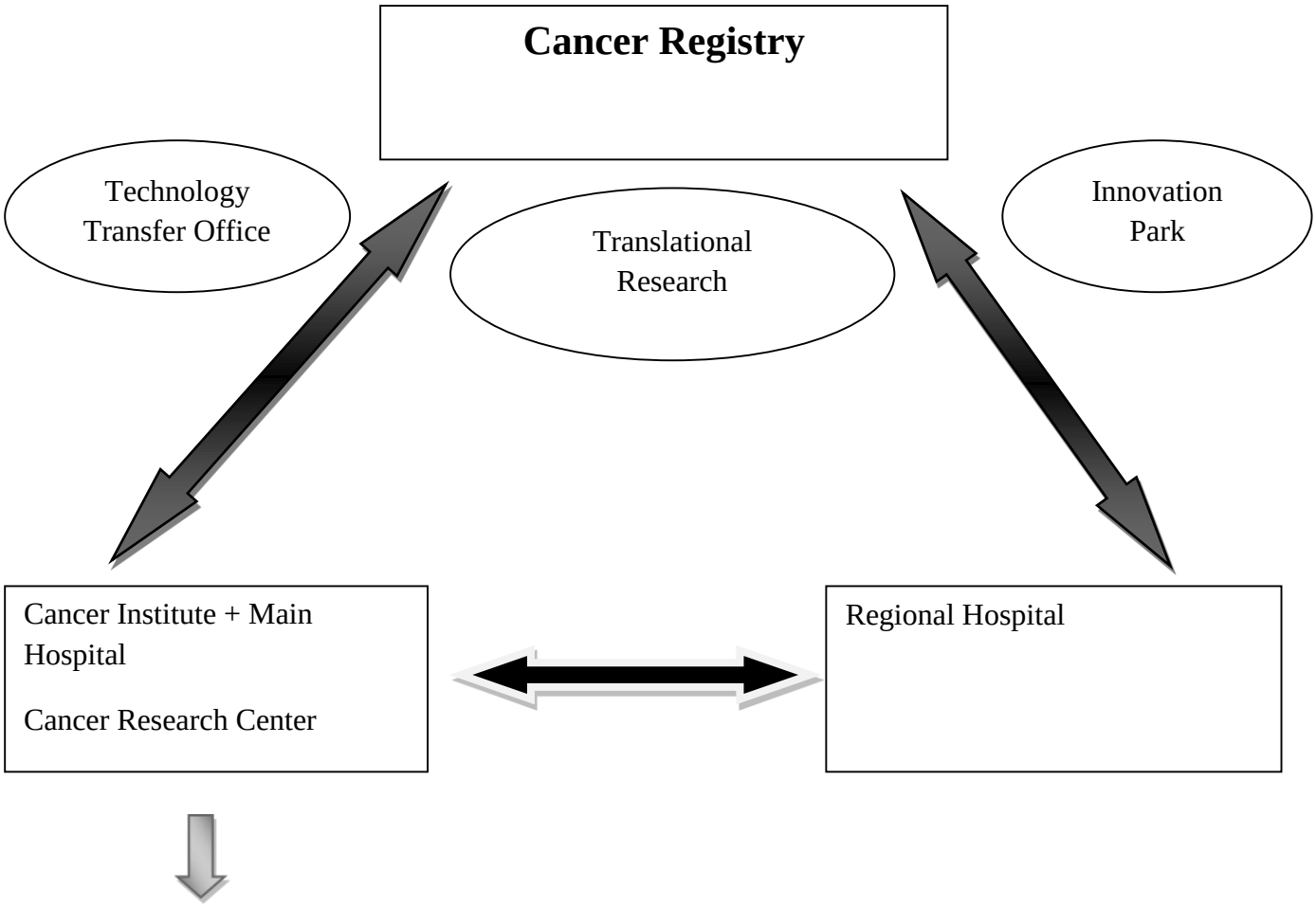
Academic & Hospital — BiotechCompanies&SpinoFFs — National pharma / Global pharma

Talent→ [Infrastructure / Interdisciplinary research] → [Funding] → → [-Marked Access; -educational Meeting]

Contract R. | Infrastructure | Work Force Education

Complete ⟶ Collaborate

# Comprehensive Cancer Center




**<u>Innovation Center/Park</u>**

1-30 Center Path way

National Standards and Guidelines

Stepwise Implementation→ GI

Breast

Lymphoma

Leukemia

2-Iranian Food Based

Dietary Guideline for cancer patients

3-Monitoring flow

Focus on bottle NECK (pathology, CT, MRI, Access to Surgery)

4-Promotion – prevention

Early detection

5-Rehabilitation

## Hospital / Cancer Institute

-General Cancer Therapy Center

-Specialized Cancer Center

-Highly Specialized Cancer Center → should be have

- -Cancer Registry
- -Pathology
- - Cancer Genetic
- -Incubator for startup compaining

-National & International Collaboration at institutional level

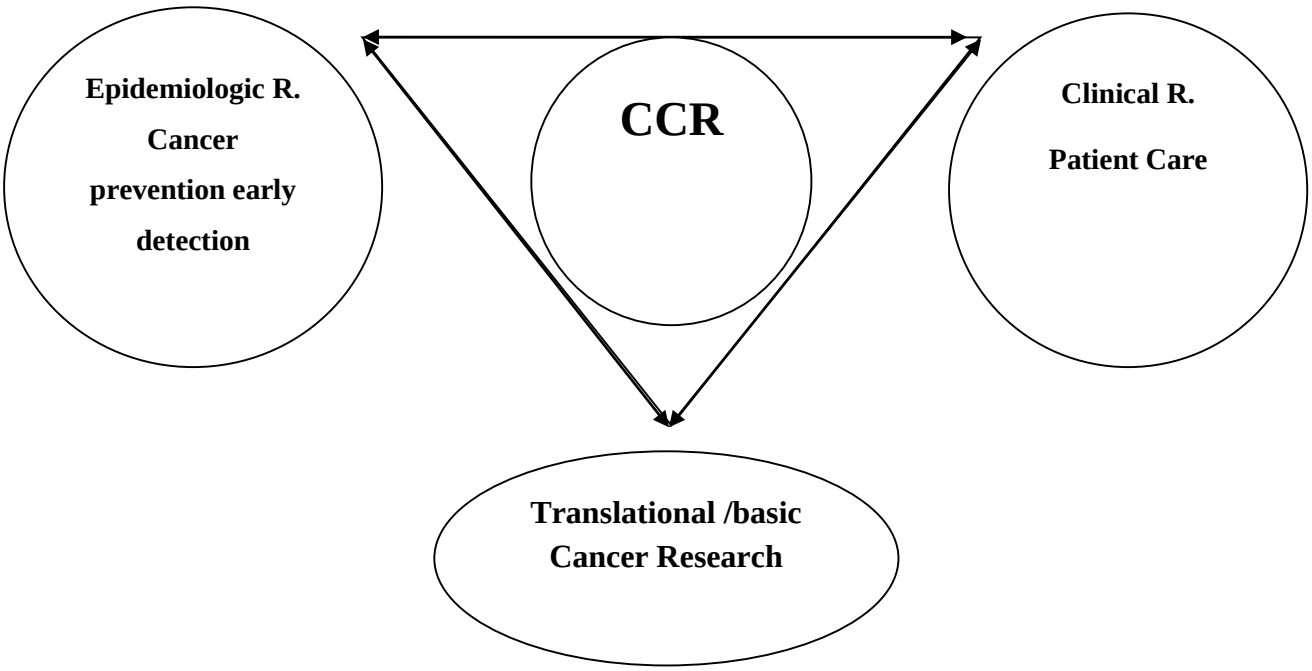
**(Sister InstitutionNetwork)**

**Iranian Cancer Consortium**

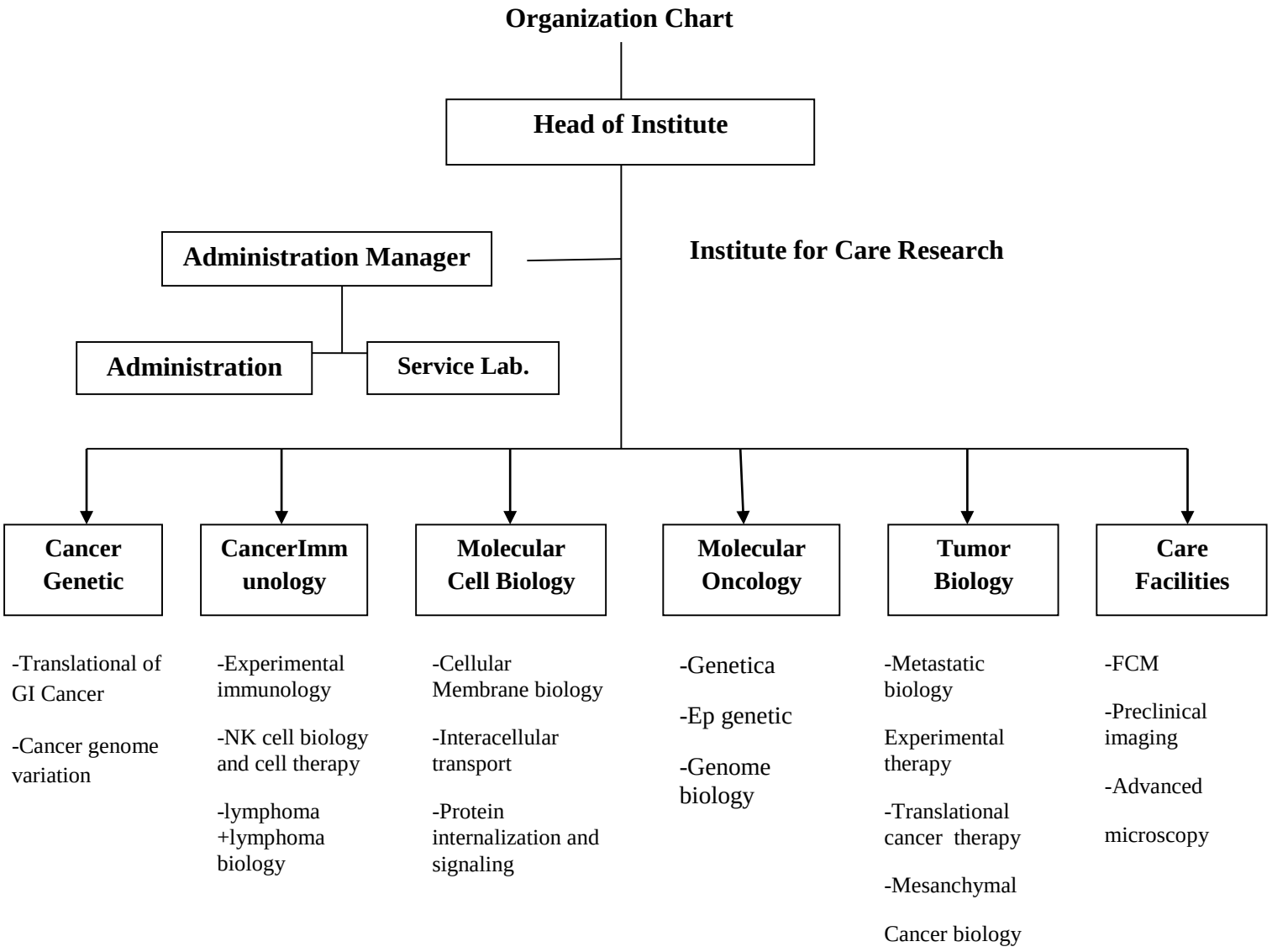
**Global Academic Programs**

**Institute for Cancer Research**

# Comprehensive Cancer Research




**Toward Funding to External Fund**




# Department

## Cell Therapy

-Dendriticcell based tumor vaccines

-T cell engineering

-CAR technology

-TCR technology

-NK cell technologies

-Immune Monitoring

# TranslationalR.

# Clinical implementation

1. GI Cancer
2. Breast
3. NHL/HL
4. Leukemia
5. Lung CA.
6. Gynecologic Cancer
7. Prostate Cancer
8. Multiple Myeloma

# Key Figures Annually

**Funding (**percent): Actual institute expenditure annually by internal/external funding forces

-Determine the corresponding figure for budget allocation

-External funding by source:

International sources- private sources-research council

**Employees** (number): Full time employees by type of position

-Management: GP- Specialist- Sub specialists

-Researchers

-Post doc

PHD students

Technical personnel

## -Completed PhDsandMasterDegrees Number

-Master`s Degrees

-PHD

## -Article published annually Number

-Scopus mean median

-PubMed mean median

-ISI mean median

About Hematology: Scopus-PubMed- ISI

About Oncology: Scopus-PubMed- ISI

GI Cancers: Others.

Articles published by Employee

-Management group as Name

-Researchers

-Post doc

-PhDs students

Technical personnel

The total number ofpeer reviewed publication annually

## Cancer genetics

**Headed by:**

**Vision/Mission**

**A.** Perform integrated molecular and epidemiological studies to reduce risk, achieve early diagnosis improve diagnosis
-To tailor the treatment for the individual patient with GI cancer- Breast- Lymphoma- Leukemia

Department Consist- Research group

Laboratory technology group

-The research focus is on molecular classification, data integration, translation and pan cancer analysis of GI tumors with a common goal of achieving a deeper molecular understanding of internal and intra tumoral heterogeneity between tumor subgroup, within a single tumor.

## Out Strategy

Has been to establish a pipline for

1. High quality biobanking and data handling of patient cohorts with long term.
2. High quality follow up data
3. Perform multi level molecular characterization done to single cell level
4. Performing integration of biological data with clinical variables, with the aim of developing prognostic and predictive signatures
5. Designing assays that can be translated into clinical management

## Vision

**B.** We should be pioneers in profiling of GI cancer, leukemia, lymphoma
-Leading clinical important molecular subtypes
-Followed by multilevel characterization of large cohorts.
-Development of computational algorithms

**C.** We should have extensive institutional, national, international collaboration
-involved in several program (consortium)

## Cancer genetic departments

**1. Molecular Biology:**

**Leader:**

**Vision:**

1. Fundamental understanding of the biological dynamics of GI cancer, Lymphoma and translate into clinical management by:

*Molecular analysis of DNA, mRNA, miRNA and protein.

*analysis of patient material –bulk tumors

-single cell

-liquid biology

*from clinical trials with sampling before, during and after therapy

*order to reach an earlier and more accurate diagnosis to improve tailoring of treatment; to predict drug response and patient prognosis, developing of new therapeutic approaches

*understand role and impact of inter and intra tumor heterogeneity, response to therapy, patient outcome

**Projects:**

1-Single level classification at DNA, RNA, protein, metabolic level of both primary and metastasis GI Cancer in large cohorts of patients + various stages of the disease from normal GI to advanced stage

2-Somatic genetics of GI cancer from single genes to genomepanels to whole genome sequencing

3-Genomic alternation to elucidate the genomic landscape

4-Intra tumor heterogeneity

5-Her2 positive

6-Genomic and functional analysis of therapeutic targets

7-Functional screens elucidating the role of miRNA

8-GlyCan and miRNA as serum biomarkers

9-Integrated classification

**Recent achievements:**

-Publication activity

-PhDs degrees

**Members:**

**2. Translational studies of cancer (GI- Lymphoma)**

+Whole genome analysis on patient material for identifying predictive & prognostic biomarkers

+analyzing mRNA, miRNA, DNA, methylation glycosylation- mutation, protein

**Aim:** personalize medicine and improve prognosis

**Projects:**1- serum miRNA signature for GI Cancer

2-Molecular characterization of GI Cancer

3-miRNA of GI Cancer

**Recent Achievements:**

**3. Cancer genome variation**

**Aim:**

1-Genome variation:

Fine mapping characterization of susceptibility lociin mitotic regulatory pathway genes and in genes shown to lead to aggressive cancer

2-DNA methylation in the early phase of disease progression and their clinical impact on treatment response

3-Integrated analysis of high resolution DNA methylation profiles, gene expression, germ line genotype clinical end points

4-Non Canonical transcriptomes

-long Non coding RNA in normal/ tumor tissue

-converse changes cancer related protein coding genes

5-Immune signaling

**4. Tumor initiating cell in GI/Lymphoma progression**

**Aim:**

1-Identify critical molecular, regulatory pathways cell types involved in development & progression of cancer

2-Focuse on earliest tumor stages

3-Role of tumor stages

- How tumor progress to more advances stages
- Improved strategies for early intervention
- More prices treatment

**Projects:**

- Characterize progression pathway of pre-invasion lesions

- Identify and test potential molecular progression markers

- Characterize genetic, phenotypic, functional heterogeneity of tumor

- Identify and test targetable markers of tumorigeniz cell population

- In study tissue homeostasis upon anti cancer treatment

- Define genetic & epigenetic regulatory events in tumor progression

**Recent Achievement**

## Cancer Immunology

**Headed by: Dr.Abedian**

**PIs:**

**Projects:**

**1. Lymphocyte biology by deciphering**

- Ontogeny of B, T, NK Cell

- Tumor heterogeneity (signaling &mutanome)

- Immune cell recognition elements (Ag discovery)

**2. Biomarkers, by profiling of**

- Lymphocytic repertoires

- Tumor and its microenvironment

- T cell receptors and humoral immunity

**3. Therapeutic, by**

- Genetically engineered T& NK cells

- Immune priming with si RNA and Ag targeting to DC

- Genetically engineered pepti bodies

- Cell therapy across HLA barrier to over one immune tolerance

- Clinical trials using local immunotherapy in Lymphoma

**1.Experimental Immunotherapy**

**Aim:**

-T cell immunotherapeutic T cell based strategies

**Projects:**

**Strategy I:** Use of T cell based alloreactivityof target self Ag

+ Identify cell type specific T cell epitopes

↓

T cell reactive with such epitopes

↓

TCR → genetic transfer in adoptive cellular therapy

**Strategy II:** Identifycationand targeting of cancer specific neo-Ag in biobank material by TCR profiling

- Identify auto-antibody targets by protein arrays

**Recent Achievements**

**2. NK cell biology and cell therapy**

-Deciphering the functional regulation of NK cells

-How (KIR) influence the function of human NK

+Integrative profiling of NK cell repertoire diversity examine the dynamic shaping of human NK report during tumor transformation, post BMT

+Harnessing adaptive NK cells in cancer therapy

**Recent Achievements:**

**3. Immunodulation and targeted therapy**

*****Blockinhibitorypathway in the immune system and tumor microenvironments via RNA; (RNA sending by immune system)

*Engineer new targeted therapeutic proteins (identify new cell surface markers) and better vaccine formulations (enhance dendritic cell function)

**Recent Achievements:**

**4. Lymphoma and lymphocytic biology**

**Aim:**

Identify biomarkers and develop novel lymphoma therapeutic strategies in Bcell/Tcell

Lymphoma, is a heterogeneous group of disease even patient with identical diagnosis have variable prognosis

**Projects:**

1-Proteomizs characterization of tumor cells and tumor microenvironment by IHC, FCM, CyTo F

2- Identify crucial mutation affect drug responsiveness (by drug assay, phospho-specific FCM, genetic manipulation)

3- Identify abnormal cell signaling by phospho-specific FCM(MCL)

4- Exome and RNA sequencing project (in DLBCL) to identify recurrent mutations, clonal evolution association with therapy relapse and disease progression

**Recent Achievements:**

## Molecular Cell Biology

Aspects of cancer cell biology:

1- Membrane traffic

2- Receptor signaling

3- Cell division

**Aim:**

-Molecular mechanisms that control cellular function related to cancer

-Control of DNA replication

cell division, growth factor signaling

cell migration, intracellular transport

**1. Cellular Membrane Dynamic**

Understand how 1-membrane dynamics contribute to tumor suppression

2-membrane dysfunction promote cancer development

**Project:**

1-A mechanism of carcinogenesis

2-Endocytosis (control of tumor suppression+promotion)

3-Tumor microenvironment interactions 4-Control of cell polarity by membrane dynamics

5-Centrosoma dynamics in cancer

6-Cytokinesis in development and carcinogenesis

7-B-catenin dysfunction complex in physiology and cancer

8-Membran dynamic in promotion of genome integrity

**2.Intra Cellular Transport**

**Aim:**

-Characterization of intra cellular transport

-Knowledge about biomarkers (Biodegradable) nano particles in cancer diagnosis, therapy and prevention of disease

**3. DNA Replication and Chromosome Dynamic**

**Aim:** Knowledge about DNA replications, moved and repaired

**Projects:**

1-Mechanism of replication forkcollapse

2-Role of B clamp and PCNA protein in replication fork rescue

3-The roles of Seq A, topoisomerases and Dam methylase in stabilization of replication fork and daughter chromosome segregation

4- The role of DNAinhibitor protein and RNA polymerase transcriptional activity in control of replication frequency

**4. Protein Internalization and signaling**

**Aim:** The main goal of the research group is to elucidate differences in mechanism of signaling induced in normal and tumoral cells by FGF

Maintenance of tissue homeostasis depend on complex inter cellular growth factor mediated fibroblast (FGF) signaling system represented one of the fundamental tool of cell to cell communication

FGFs-FGFRs signaling system exerts a powerful combination of biologic effects during development and maintaining of malignancy, strongly oncogenic central drive of tumor progression, as mediators of the mesonchymal-epithelial transition, tumor cell survival, migration, metastasis neoagniogenesis

-FGF induced signaling a promising target for cancer therapy

## Molecular Oncology

Molecular evolution of solid tumor particularlyGI cancer

**Needs:**

-High quality biobanking

-Protocols / study designs development

-Expectations

-Patent applications

-Innovation grants

-License agreements

**1. Genetics**

About: Identify clinically important molecular biology and that predictive / prognostic for GI Cancer in the complex dynamic of cancer development

**Projects:-**Molecular biology⟶biomarkers identification

- Genomic tumor heterogeneity and clonal evolution
- miRNA expression
-Identification of drug targets and sensitivity by invito

**2. Epigenetic**

Studying DNA methylation alternation in GI cancer

**Aim:** Identifying biomarkers with clinical impact biology
Understand and analyzing the underlying of these aberration

**Projects:**
- Epigenetic sub classification for GI cancer
- Mechanism of DNA methylation machinery
-Methylom based detection and monitoring
-Epimutation and epigenetic drivers of tumor development

**3.Genome biology:**

+ Mutation analysis for identify critical genes (genomes & transcriptomes) for development of cancer (Diagnostic / prognostic)

+ Modelling heterogeneous solid tumors

# Radiation Biology

**Vision**→ 1- Basic Radiobiological research for understanding of response to ionizing and Non-ionizing radiation on molecular, cellular, physiological level

2- Translational and clinical studies for design new strategies for diagnosis and treatment of cancers

**Goals:** 1- Understand molecular and physiological mechanisms of post radiation ($\gamma$- UV, visible light)

2- To utilize knowledge for new radiation based treatment regimens with improved specifity and efficacy toward GI cancer

3- To develop non ionizing radiation therapy combined with photosensitizing agents, via direct tumor cells kills or internalization of therapeutic or sensitizing agents

**1. Photochemical (PCI) Internalization**

Light induce → photosensitizer release from endocytic vesicles rupture →there by release of macromolecules into cytosol

1-Designe and develop recombinant immunotoxins based on type I ribosome in activation protein

2-Reveal the PCI technology for GI cancer

3-Utilize new vehicles for targeted therapy of small molecular drug to endocytic vesicles

4-Evolution of the vasculature as a target for PCI treatment

5-Document and utilize the anti-tumor immunity potential of the PCI technology

6-Develop PCI as a strategy for boosting anti cancer vaccine

**Projects about photobiophysics**

Public health strategies regarding sun exposure, skin cancer, VitDstatusand sun protection

**Project:**1-cutaneous VitD synthesis versus skin cancer development

2-Role of UV radiation in skin cancer

3-VitD level and cancer

**2. Cell-cycle Regulation in Eukaryotes**

Characterize the molecular mechanisms regulating cell-cycle progression in the model organism yeast and mammalian cells in culture

**-Characterizing a check point**which involve kinase Gen2 activation and protein translation

-Regulation of $G_1$-S, $G_2$-M translation in yeast cells and mammalian cells

-Regulation of translation of the stress

-The activation mechanism of Gen2 in cancers

**3. Clinical Radiation Biology**

**A.** To develop molecular biomarkers that identify patient at risk of radiotherapy failure

- Based on tumor biopsies and blood samples collecting at diagnosis and during therapy
- Whole genome methodology → microarray +sequencing technique
- Develop biomarkers for personalized radiotherapy

**Projects:** 1- Genetic alternation and chemoradio resistance of GI cancer

2-Molecular hypoxin biomarkers in GI cancer

3-Combined molecular and imaging biomarker (PETScan) in GI cancer

**4. Radiation Biology and Tumor Physiology**

-Mechanism causing tumor resistance to RT consequence of microenvironmental abnormalities

**Aim:** Develop strategies for personalized RT of GI cancer

**Projects:**1- Mechanism governing the microenvironment and radiocurability of tumor

2- Interstitial fluid pressure and hypoxin in tumor

3- Preclinical and clinical MRI

4- Develop anti angiogenetic treatment for physiological microenvironment of tumor for enhancing RT

**5. Radiation Biology and DNA Signaling**

Ionizing radiation cancer DNA damage signaling cascades influence cell death or DNA activation repair system and cell cycle check point (S-G2) that recognize knowledge used for inhibition of check point → improve therapy cancer

**Projects:-** Preclinical explorationof check point kinas inhibitor ($CHK_1$, Weel, Atr, $p_1k_1$)

- Functional role of protein $phosphatas_1$ ($DP_1$) targeting sub units irregulation of check point

- Identification of Novel regulator of DNA damage

- Function of the centrosome and centrosomal protein in cell cycle

## Tumor Biology

+ Investigation on biological mechanism of metastatic progression

+Research program

**Translational Research**

- Cancer genomics
- Computational science
-Biological mechanism of metastasis

+Collection of patient derived tumor models

+Use for biological studies of disease progression

**1. Metatasis Biology and Experimental Therapeutics**

Metastasis is major clinical challenge

**-Projects:**

**A.** Basic research revealing mechanism of metastasis or treatment resistance

-Proteins and regulator with tumor stroma interactions and effects on invasion, metabolic state and immune response

**B.**Preclinical research for Novel drug or drug combination

1- Invivo&invitro studies for efficacy and mechanism

2- Biomarker detection by molecular and functional technique (PET-MRS-MRI)

**C.** Clinical trial for precision medicine

**2. Translational Cancer Therapy**

- Basic, translational and interventional methodology

-Competencies spanning from basic biologist through translational scientist to clinician

-Methods from Biochemistry and cell biology, preclinical drug testing in animal models, biomarkers studies in clinical cohorts and interventional clinical trails

Example: - Exome in cancer metastasis

- Met action clinical trial

- $B_7H_3$ protein in Met

- Experimental models and therapy in GI cancer

**3.Computational Cancer Genomics**

Using high through put genomic technologies and computational modeling for understand signaling system

Use of well characterized panel of tumor cells in different stage of progression as chart causative molecular factors to build lad model of GI cancer addressed are immune aspect, chromatin including 3D models of nuclear DNA, mutational processes and signaling modeling

*Implementation of computation aspects of sequencing toward diagnosis

**4. Mesanchymal Cancer Biology**

+Biobanking and genomic characterization of patient material

-At least 500 samples

+Preclinical investigation: invitro&invivo models for therapeutic potential of target mutation

+Tumor Biology: | Development and progression

Identify biomarkers

+Studies of metabolic reprogramming

+Implementation of sequencing in diagnosis

+Exploration of liquid biopsy, detection of tumor derived DNA in blood for monitor disease progression and therapeutic markers

**Mazandaran Cancer Registry (MCR)** is a population-based cancer registry whose goal is to collect particular data on all cancer cases diagnosed in population covered by MazandaranUniversity of Medical Sciences(MAZUMS).

The registry is located within the comprehensive cancer Center and is responsible for maintaining cancer incidence reporting system in covered population; monitoring data accuracy, reliability, and completeness through systematic quality assurance procedures; analyzing cancer incidence and mortality data; disseminating cancer information and facilitating studies related to cancer prevention and control.

Cancer Registry data are used to identify populations at increased risk of cancer, investigate public concerns of suspected excesses of cancer due to environmental or other factors, and monitor trends in cancer incidence and mortality so that appropriate interventions can be done.

**Mission Statement**

The mission of Mazandaran Cancer Registry (MCR) is to serve the public by collecting, analyzing, researching and disseminating quality cancer data to help describe the burden of cancer, so all cancer prevention and control programs can be implemented to reduce cancer incidence and mortality in covered population.

**Vision Statement**

Cancer prevention and control, improving diagnoses, treatment, survival and quality of life for all diagnosed cancer patients in covered population.

**Values:**

**Confidentiality:** The actual information contained within the medical record is the patient's property and cannot be released to anyone without proper authorization from the patient.

**High quality data assurance including:**

a. Completeness: The proportion of stored data against the potential of "100% complete"

b. Uniqueness: Nothing will be recorded more than once based upon how that thing is identified.

c. Timeliness: The degree to which data represent reality from the required point in time.

d. Validity: Data are valid if it conforms to the syntax (format, type, range) of its definition.

e. Accuracy: The degree to which data correctly describes the "real world" object or event being described.

f. Consistency: The absence of difference, when comparing two or more representations of a thing against a definition.

**Passion:** We are passionate about preventing cancer and improving surveillance.

**Goal:**

Population-based cancer registry establishment in population covered by MAZUMS.

# Cancer Epidemiology

## A. Measuring Disease Frequency

### 1-Prevalence and Incidence rate of all Cancers

Descriptive epidemiology

Prevalence: Number of people at point time (End of time)

Total population

Incidence: Number develop (during)

Average population

For measure **P** need cross sectional study and for **I** need to start with group (cohort)

### 2-Population at risk: Breast, GI & Cervical cancer

**Problem= Different reports used the same definition of disease**

### 3- The relationship between incidence and prevalence

**P ≃ I x D** (average duration of disease)

**Question:**If a new treatment were developed for a disease, what effect would this have on the prevalence and incidence of the disease?

**Balance between Immigration and Birth**

$$\frac{P}{I-P} \simeq I \times D$$

**4-Cumulative Incidence (CI) ~ Attack Rate**

$$\mathbf{CI} = \frac{\textbf{Number of developed disease in a specified period}}{\textbf{Number of Risk}}$$

$$\mathbf{IR} = \frac{\textbf{Number of developed disease}}{\textbf{Number of person-years at risk}}$$

## Cumulative Incidence

In clinical Trial
- EER= Experimental Event Rate
- CER= Control Event Rate

- Crude MR/ Specific MR of Cancer/100% per year
- Crude IR/ Specific IR of Cancer

Age specific incidence and mortality

Different age structure with varies ill and dying age

(SIR-SMR)

***Standardized incidence and MR (Mortality Rate)**

Direct Standardization:

Indirect Standardization:

Standardization based different age & sex, different time period

***Proportional Mortality Rate (PMR)**

Measure of relative importance of particular cause of death in a given population used when there is insufficient information for calculate SMR

***Case fatality ratio (CFR)**

-Proportion of people with give disease who die in given short time period

-Severity of Cancer

-Direct assessment of the effectiveness of intervention

***Survival rate and relative survival rate adjusted to age**

Life expectancy and healthy life expectancy

Average number of years that expected to live & current mortality rate continue

Healthy life expectancy (HALE): Healthy Adjustment

**Disability- adjusted life expectancy:**

Number of years can expect to live free of disease

**Years of potential life lost (YPLL)**

Measure of premature mortality

Expected years of life lost

Health adjusted life years (HALYS)

Disability- adjusted life years: estimate loss of healthy life

Quality- adjusted life years.