# Nanoenzyme Therapy For Colorectal Cancer

**Running title**:   Intestial bowel cancer

**Maira Shahzad[1†], Nabila Farah[1†], Ayesha Raiz1[\*], Shahzad Bashir[2]**

[1]*Instiute of Molecula Biology and Biotechnology, University of Lahore, Lahore, Pakistan*

[2]*Departmentt of Biochemistry, University of Minhaje, Lahore, Pakistan*

[†]Contributed equally to this work and are co-first authors

**Novelty statement**

Nanomaterials have noteworthy applications in nanobiotechnology, particularly in diagnosis, drug delivery systems, prostheses, and implants. Nanoscale materials integrate well into biomedical devices because most biological systems are also nanosized. Nanozymes are nanomaterial-based artificial enzymes. Nanozymes can be used to detect ions, molecules and organic compounds both qualitatively and quantitatively. They have also been applied for destruction multi-drug resistant bacteria and the degradation of various organic pollutants.

**Abstract**:

Nanotechnology has developed as an encouraging field to wage war against cancer. The formulation and utilization of nano-scale nanomaterials including nano enzymes or nanoparticles for cancer therapeutics are known as cancer nanotechnology. Colorectal cancer or large bowel cancer is the prominent reason for cancer-associated deaths worldwide. Practical and targeted nano enzymes that could be well being from various highly expressed receptors on the surface of tumor cells offering anticancer bioactive. Nanoenzymes minimize the adverse effects of cancer and help in diagnosis on time so reducing the mortality rate. More polyps are benign at different sites in the intestine but their timely diagnosis prevents them from malignant. Nanoenzymes prove beneficial in cancer theranostics.

## 1.Introduction:

The small intestine and large intestine both are the two main components of the digestive tract and uncontrolled proliferation of the cells of small and large intestines are referred to as cancer of the respective parts. Hematologic and solid tumor cancer are two main classes of cancer other subclasses belong to both of these. Small and large intestine cancer relates to the solid tumor cancer group because it can create tumors in any tissue or part of the body. For instance colorectal, prostate, lung, and breast cancer, etc. Metastasis is an important term in cancer if cancer spread to another part of the body then it is referred to as metastasis. While the tumor is an outgrowth and may be cancerous (malignant) or benign (non-cancerous).

Intestinal cancer also known as small bowel cancer and very subtle and hardly recognized in 1% of new cancer diagnoses. The longest part of the digestive tract is the small intestine and almost 90% of absorption is done here. It has mainly three components duodenum, jejunum, and ileum. It is an almost 22 feet long tube that covers the complete digestion of the food and somehow absorption. It is a very rare type of cancer and due to its uniqueness and less occurrence, it is studied less by researchers, and understanding about this is not common. Small bowel cancer consists of 40 distinctive and complex subtypes. Some of them are adenocarcinomas, lymphomas, sarcomas, and carcinoid tumors. (Pan and Morrison ., 2011)

75% of the gut comprises the small intestine. Alteration in the beta-catenin pathway which plays role in cellular homeostasis has been observed in SBA. The mortality rate of small intestine cancer is very less. Data record from different states displays their rarity and complexity for example the American data record of 2018 depicts that the death rate of this rare cancer type is only 0.2%. IBD

(Inflammatory bowel disease) in patients in a chronic state leads to small intestine cancer. (Chen, Chen et al.,2021) Some common indications of small bowel cancer included abdominal pain, weakness, anemia, and jaundice, after eating severe pain. Men suffer more from small bowel cancer in contrast to women. People who have more gluten in their diet are at the edge of having small intestine cancer. The patients with Crohn's disease which immune system invades the cells of GIT and destroys them. Use of expired drugs and alcohol consumption have small intestine and large intestine major attacking sites. (Zeino et al., 2010) There are almost thousands of microbiota present in the alimentary canal that aid in digestion but their numbers and activity vary according to environmental factors, eating habits, exercise, inherited conditions, consumption of antibiotics, prebiotics, intake of addictive drugs, and a lot more. The researchers after research for many years come to the point that any dysregulation or dysfunction of microbiota leads to many small bowl disorders. The severity of small intestine disorders leads to malignancy which is fatal. (Allocati et al., 2013) There is a relationship between cancer, microbiota, and environment. Helicobacter Pylori plays a drastic role in developing gastric carcinoma.(Amieva & Peek, 2016) The small intestine disease may be genetic or acquired. Sometimes benign polyps show no symptoms these are lipoma, hamartoma, and desmoid tumor. Some genetic disorders like familial adenomatous, and polyposis coli are also in coordination with the producing small intestine. Small bowel cancer symptoms do not occur at once it may take months to appear. (Gill et al., 2001).
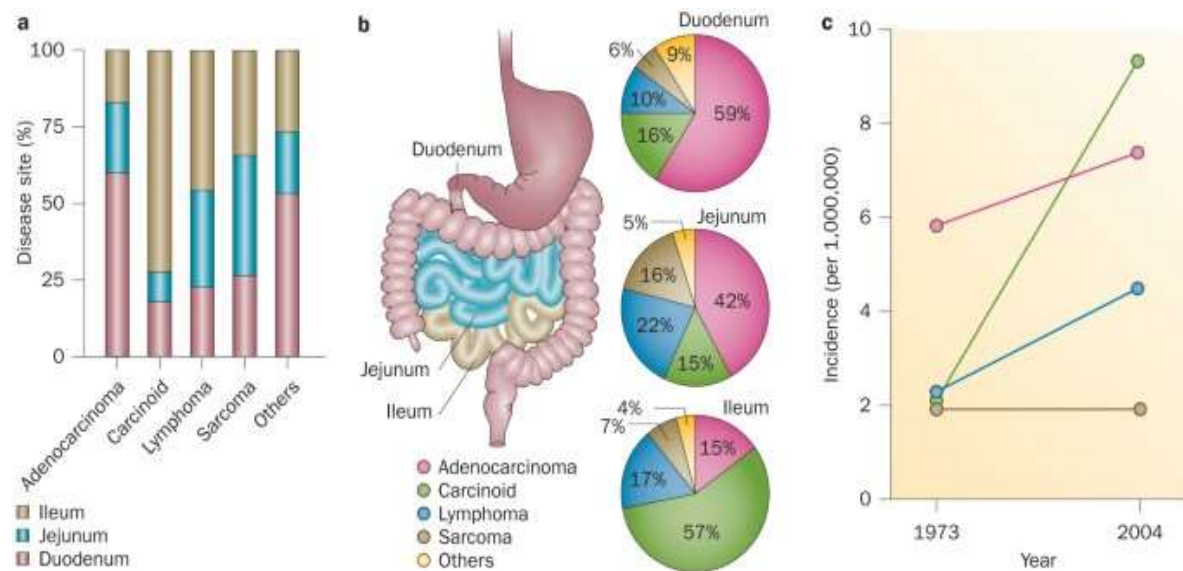
Fig 1: Localization of Small Bowel Cancer

The large intestine or Colorectal cancer is one of the most notorious forms of cancer that is the second most reason for death. Cecum, colon, and rectum are three parts of the large intestine. Colon cancer and rectum cancer both have almost the same symptom s that's why it is collectively known as colorectal cancer. The epithelial cells of the colon or rectum are the origin of colorectal cancer and the emergence of cancer occurs due to defects or mutations in the cellular signaling pathways. These mutations may be genetic or acquired. (Abdul Khalek et al., 2010) The position of the tumor whether it may benign or malignant in the large bowl exhibits the symptoms of colorectal cancer. Patients with a bleeding rectum or anemia are at high risk of colorectal cancer. The chances of having colorectal cancer start at the age of 50. 37000 colorectal cancer cases are reported every year in the United Kingdom. (Morson & Bussey, 1970) . A report published by the American Society of Cancer displays that colorectal adenocarcinoma accounts for 96 % of. The symptoms of colorectal cancer include diarrhea, severe constipation, weakness, change in the color of stool, or bleeding. There are some stages of colorectal cancer stage 0, stage 1, stage 2, stage 3,

and stage 4. Stage 0 is the very initial stage of cancer diagnosis at this stage then it is fully treatable. While stage 4 is the stage where cancer metastasis to the adjacent parts of the body. A person having benign polyps is at great risk of having colorectal cancer. A sedentary lifestyle, poor eating habits, mutations in genes, other cancers, low fiber intake, low fruit and vegetable use, HCV, HBV infection, smoking, alcohol consumption, radioactivity exposure, pyloric infections, and severe gut-related diseases are the main risks factors of colorectal cancer. (Feng et al., 2019)
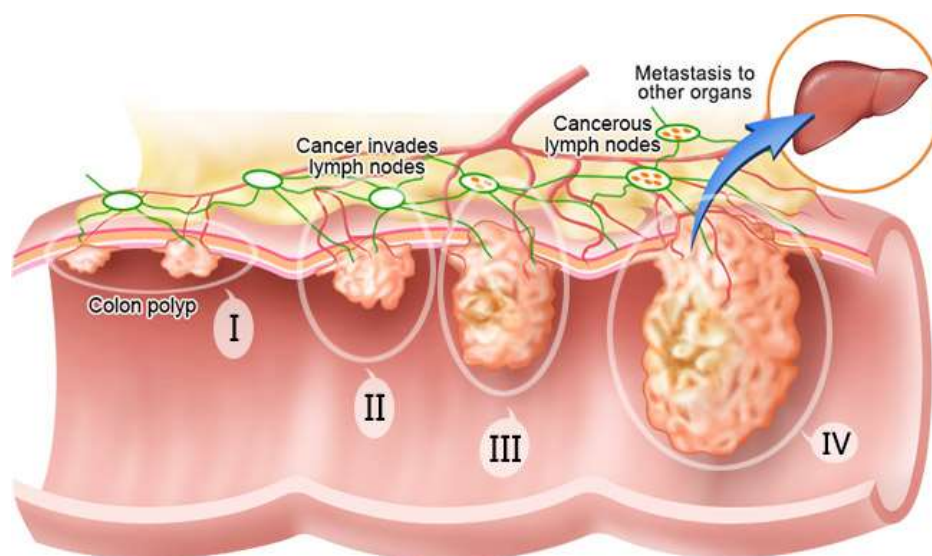


Fig 2: Stages of Colorectal Polyp

According to the dataset reported by China National Cancer Center, large bowel cancer is the fifth most reason of mortality worldwide. (Zuo et al., 2020) Mutations in several hydrolytic and reductive bacterial enzymes in the colon are also leading causes of lesions in the large bowel that cause cancer. The fat-rich diet increases the risk of proximal cancer. Intake of calcium minimizes the risk of cancer but excessive consumption of vitamins like folate and calcium increases the risk of metastasis. Colorectal cancer can be classified as proximal and distal sites of the colon.
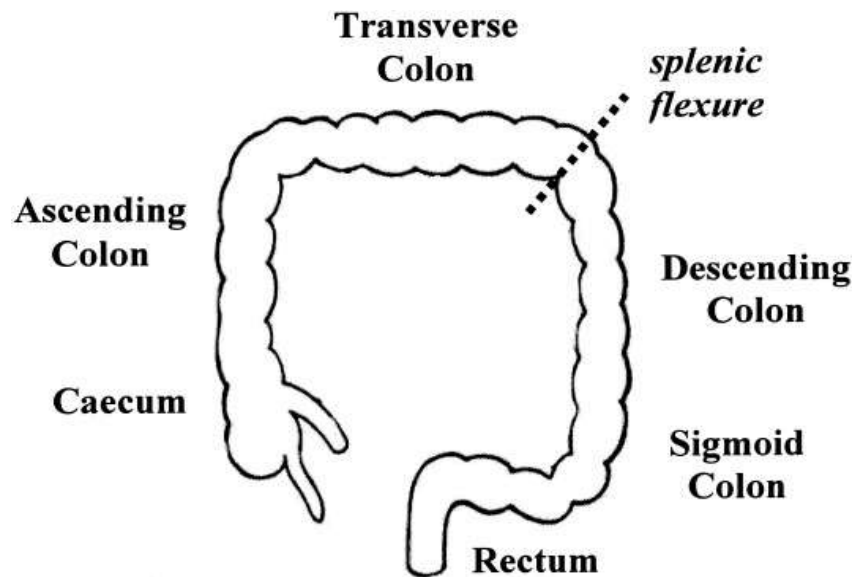
Fig: 3　Right and left-sided tumors categorized in the large intestine

In the above figure caecum, ascending colon, and transverse colon are categorized as right-sided tumors that have proximal sites related to splenic flexure while left-sided polyps including descending colon, sigmoid colon, and rectum are at distal sites related to splenic flexure. (Iacopetta, 2002)

**Cancer Therpeutics :**

The most familiar type of treating intestinal or any other type of cancer include:

➢ Surgery

➢ Chemotherapy

➢ Radiation Therapy

➢ Hormone Therapy

➢ Immunotherapy

➢ Stem Cell Transplant (Bone marrow Transplant)

➢ Hyperthermia

- ➢ Photodynamic Therapy

- ➢ Targeted Therapy

In surgery, the cancerous tissue is removed from the body. In chemotherapy, the cancer cells destroy with some medications, and in radiotherapy cancer cells kill with the aid of high-energy x-rays. While in hormonal therapy metastatic cells are blocked from acquiring the hormones that are essential for growth.(Zugazagoitia et al., 2016) In immunotherapy body's immune system boost up against the cancerous cells and this handles the adverse effects of metastasis. While bone marrow transplant is commonly used to cure leukemia, anemia, and lymph node cancer where bone marrow cells are replaced. In targeted therapy physicians only target the malignant cells and polyps and prevent them to invade other cells. Photodynamics is not much old technique in which drugs that are actuated by light only destroy the malignant as well as atypical cells. Body tissues are piping hot for the destruction of cancer cells and it does not harm the normal cells this technique is hyperthermia. (Ahles et al., 2012)

**Complications:**

After cancer treatment, many complications may happen to a person. There are variations in complications associated with people that have the same type of cancer. Age, immune system response, gender, lifestyle, and sometimes causes are also different but there are some common variations (Tebbutt et al., 2003). Some common variations are the following :

- ➢ Anemia

- ➢ Alopecia (Hair Loss)

- ➢ Nausea and vomiting

- ➢ Skin issues

- ➢ Thrombocytopenia

- ➢ Inflammation and pain

- ➢ Sexual health issues

- ➢ Infertility

- ➢ Diarrhea etc

**Recent Provocations in Cancer Treatment:**

**Accurate Oncology:**

This consists of molecular genetics in the diagnosis and treatment of malignancy. In this new technique, only the affected area is targeted and unlike chemotherapy, it doesn't harm the healthy cells. (Boellaard, 2018)

**Indication in DNA of Cancer Cells:**

According to a report published by the Cambridge University Hospital England, the 12,000 patients' malignant cells indicate novel indications that cause cancer. Almost 58 new alterations were observed in cancerous cells. (Huang et al., 2020)

**Liquid and Synthetic Biopsies:**

Biopsies are the procedures to diagnose cancer but it is very protruding and required a piece of the body both liquid and synthetic biopsies are used to examine malignancy. The most usual types of biopsies include incisional, excisional, and needle biopsies. The healing time from biopsies is almost 2-3 weeks.(Siravegna et al., 2017)

**Car-T-Cell Therapy:**

Chimeric antigen receptor therapy is a comprehensive and effective treatment in cases of cancer, especially blood cancer. In this procedure T cells of patients are taken and altered genetically to make them more immune to cancer. This is also a revolutionary treatment for fighting the battle against cancer.(Sterner & Sterner, 2021)

**Artificial Intelligence:**

A very popular and pleasant advancement in the treatment of cancer is artificial intelligence. The use of machines and computer systems for the assumption of human intelligence processes. For the treatment of cancer artificial intelligence plays a vital role in three ways detection, characterization, and monitoring(Bi et al., 2019)
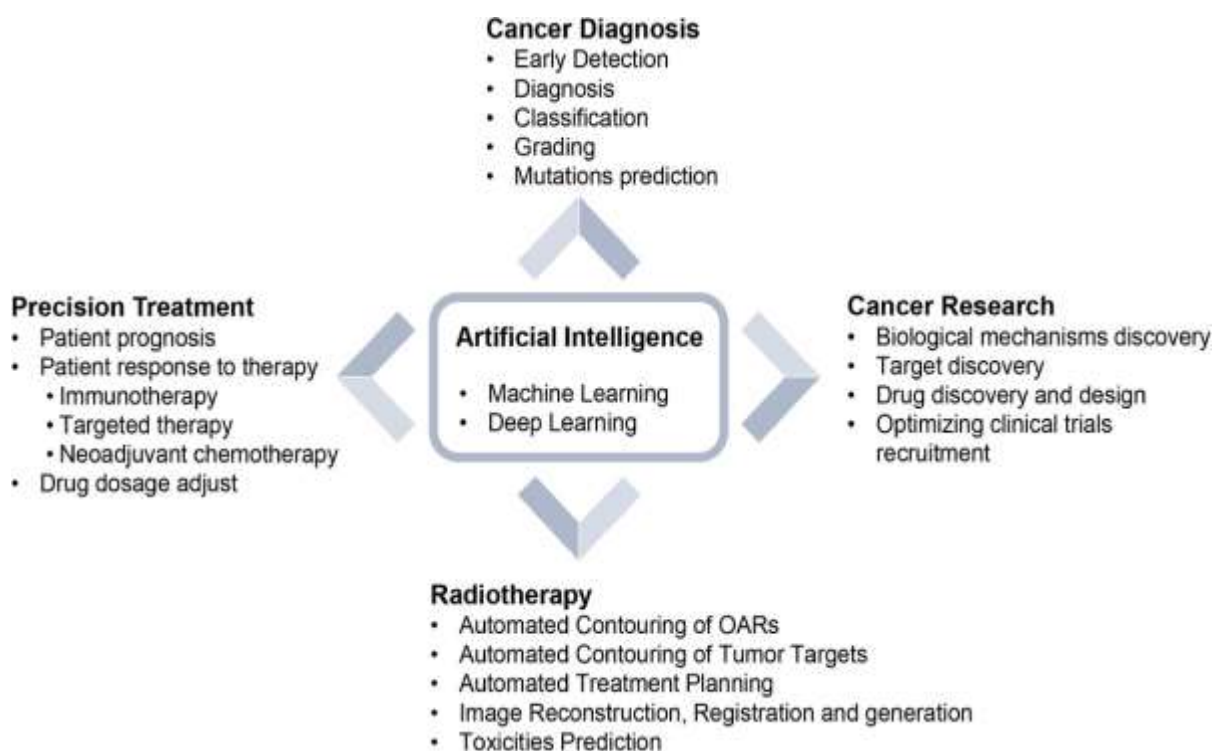
**Cancer Diagnosis**
- Early Detection
- Diagnosis
- Classification
- Grading
- Mutations prediction

**Precision Treatment**
- Patient prognosis
- Patient response to therapy
  - Immunotherapy
  - Targeted therapy
  - Neoadjuvant chemotherapy
- Drug dosage adjust

**Artificial Intelligence**
- Machine Learning
- Deep Learning

**Cancer Research**
- Biological mechanisms discovery
- Target discovery
- Drug discovery and design
- Optimizing clinical trials recruitment

**Radiotherapy**
- Automated Contouring of OARs
- Automated Contouring of Tumor Targets
- Automated Treatment Planning
- Image Reconstruction, Registration and generation
- Toxicities Prediction

Fig: 4   Artificial Intelligence and Cancer

**2. Nanoenzymes:**

Fabricated organic molecule or ion that regenerates the role of enzymes. We also define nano enzymes are nanomaterials that have properties related to enzymes. Natural enzymes have a binding site which is an active site that aids in enzyme-substrate attachment. But artificially synthesized enzymes contain precise receptors like crown ethers, calixarene, cyclodextrin, etc for substrate enzyme complex. (J. Wu et al., 2019)

Some types of nano enzymes are the following:

- ➢ Carbon-based nano enzymes

- ➢ Metal oxide-based nano enzymes

- ➢ Peroxidase nano enzymes

- ➢ Catalase nano enzyme

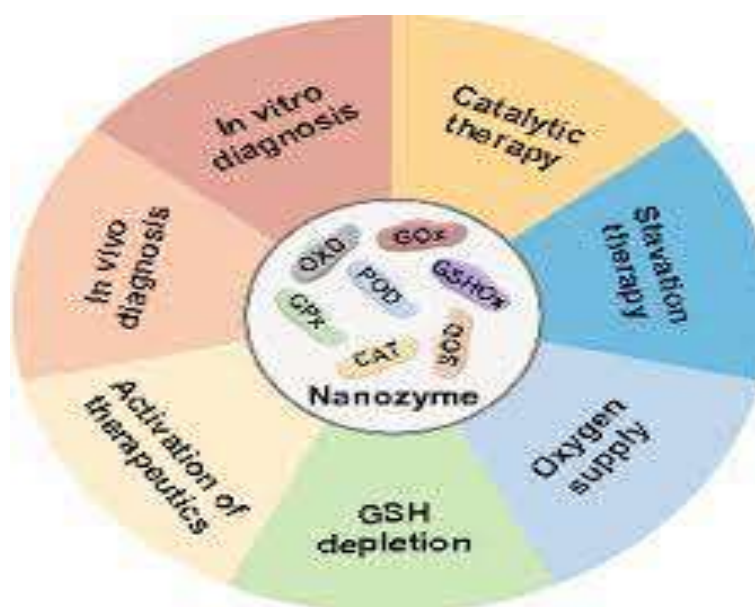- ➢ Superoxide nano enzyme  (Liang & Yan, 2019)

Fig:5 Nanoenzymes and their activities

Nanoenzymes have antitumor effects by adjusting the homeostasis of the cell. They regulate immunosuppression by stimulants of peroxidase, catalase, oxidases, etc. (Liu et al., 2021). Nanoenzymes have some attributes that make them unique in many senses like they possess high catalytic activity which is tunable and many types. Their stability is very high. Nanoenzymes have some limitations also they have limited substrate selection, potential nonpoisonous, size, shape, structure, and composition-based conditional attributes. They have insufficient standards and reference material.(R. Zhang et al., 2019)

**Nanoenzyme Therapy in Small And Large Bowel Cancer:**

Solid tumors contain malignant cells and TME. It was considered in cancer therapy that cancer cell physiology is essential but recent verifications show that tumor microenvironment is as necessary as malignant cell physiology. TME includes fibroblast, immune cells, glial cells, etc. TME can be renewed by the cancer cells to metastasize. (Ho et al., 2020) Passive and active targets are nanotechnology-based tumor targets. Some particular receptors that are highly expressed in cancer cells are related to the active target.(Fokong et al., 2012) Drug sensitivity and biomarkers are also deeply monitored by nano enzymes. Folic acid receptors on cancer cells are targeted by the folic acid-modified nano enzymes that destroy cancer cells. Porous platinum nanoparticles on graphene oxide are duplicated peroxidase in their activity. (L.-N. Zhang et al., 2014)
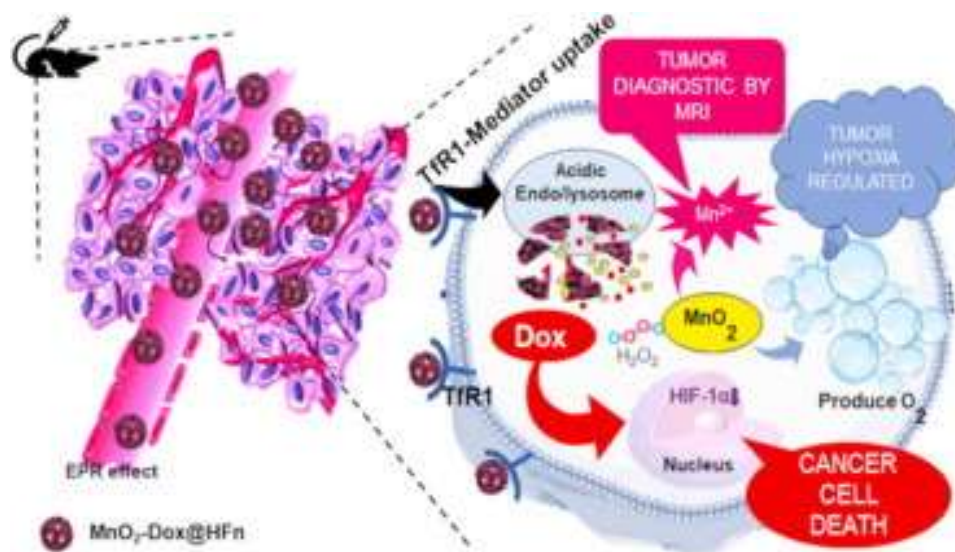
Fig: 6 Inborn tumor-targeted enzymes controlling hypoxia for cancer Therapeutics

By improving TME anti-tumor effect can be achieved. Apoptosis of cancer cells can be done by pyrite and high-affinity $H_2O_2$ initiate glutathione. (Kotov, 2010) Research on the use of nano enzymes and nanotechnology's role in small bowel cancer is limited and there is not much work is done on the small bowel cancer treatment by nano enzymes. Mutations that occur in small bowel carcinoma found that the expression level of VEGF is 96% and EFGR is 71%. There are somatostatin receptors. To find the attributes and molecular makeup of neoplasm that give vital information for the production of new nano enzymes or nanoparticles that target the cancer cells. According to researchers, nano enzymes are the combination of conjugated nano enzymes with the assimilation of therapeutic agents that may cease the development of cancer cells. Coupling nanoparticles with tumor vasculature overexpression of VFGF.(Vyas et al., 2014)

Colorectal cancer can be treated with iron oxide-based nanoparticles or nano enzymes. Human serum Albumin nanoparticles that bioactivated by conjugation with colon tumor targeting agents

which are peanut agglutinin and anti-carcinoembryonic antibodies. There are some nanoparticles or nano enzymes that modify or produced according to the tumor activity. (Ma et al., 2021)
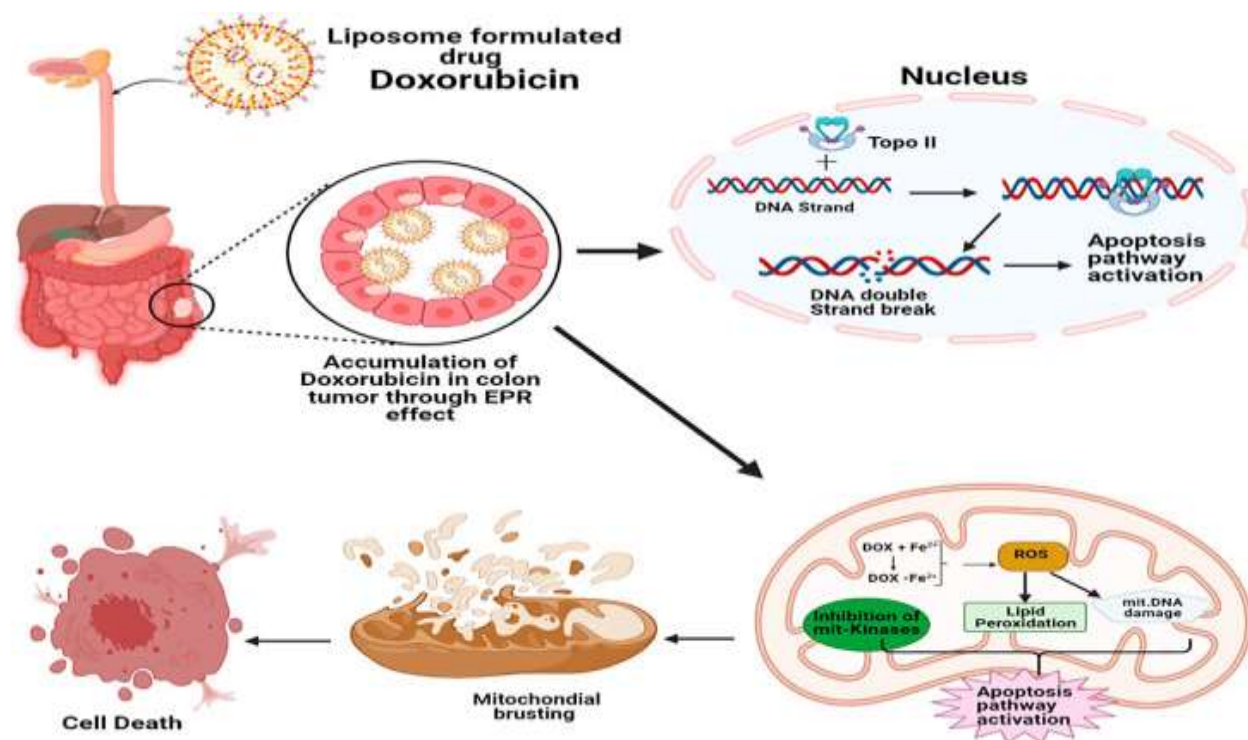


Fig: 7  Nanotechnology in colorectal cancer

Mutations in tumor suppressor genes are the main reason for neoplastic polyps that developed from the cancerous stem cells and are the main reason for causing colorectal cancer. The rate of their proliferation is very high (Desai et al., 2020). Multiple pathways at the molecular level help in proceeding with colorectal cancer. The main pathway around all cancer types is almost the same which is chromosomal instability and due to this loss of function of tumor suppressor genes. Surgery is a good option for managing nonmalignant tumors. But in malignancy cases, other recommended treatments are followed by not neglecting the polyp's size, shape, volume, etc. Nanoenzymes production has regenerated cancer management and control and it is one of the great

revolutions in the treatment of cancer. (Younis et al., 2022) Over the past 50 years, the discovery of nanoparticles working as nano enzymes used as antitumor agents is very much pleasure in cancer therapeutics. FDA approved the liposome-based nanoparticles that use in the treatment of colorectal cancer in humans. Oxaliplatin or irinotecan are chemotherapeutic agents in colorectal cancer therapeutics. Polymeric nanoparticles are the most common and most efficient nanoparticles in the treatment of cancer.(Cisterna et al., 2016)

On the surface of the nanoparticle, the conjugation of ligands play role in the formulation of targeted nanoparticles that aid in malignant tumor therapeutics. Those nanoparticles that possess the ligand on the surface are termed target nanoparticles. CRC targeting nanoparticles and monoclonal antibody is a developing field in the cancer notorious world. Some biomarkers like IGF-IR, Apolipoprotein, tyrosine kinase transmembrane, hyaluronic acid motility, and integrin(Gunasekera et al., 2009)

Targeted Nanoparticles For Colorectal Cancer

| Formulations | Ligand | Target | Cell population |
|---|---|---|---|
| Dextran and superparamagnetic iron oxide nanoparticles | Antibody | CEA | High CEA expressing cell line and low CEA expressing cell line |
| Conatomumab AMG 655 coated nanoparticles | Antibody | DR5 | HCT116 CANCER CELLS |
| Gold and iron oxide HNPs | scFv | A33 Antigen | LIM 1215 cells and nonantigen expressing |
| T22Empowered protein only nanoparticles | 18-mer peptides T22 | CXCR4 | Hela Cells |
| Chitosan nanoparticles encapsulating oxaliplatin | HA | HA Receptors | Colon cancer H29 |

| HPMA Copolymer doxorubicin conjugates | Peptide GE11 | EGFR | HT29,SW480 AND A431 Cell lines |
| --- | --- | --- | --- |
| Poly(lactide–coglycolide)NP loaded-with camptothecin | Antibody | Fas receptor | HCT116 Cells |

Table: 2

Most benign tumors when left untreated developed into cancerous tumors. Sometimes lack of facilities the diagnosis of polyps is not done on time and this neglection and poor detection leads to benign tumors into a malignant tumors. (Testa et al., 2018) Surgery is the initial treatment option for the beginning of the tumor but carelessness in this serious issue can be fatal. It is necessary to vanish this disease from the root but sometimes it may develop again after treatment and this is because the terms and conditions of colorectal or any type of cancer may vary from person to person and recovery time and healing also vary. There are also some abnormalities and side effects that are common in colorectal patients but unlike these, there are different symptoms and rare abnormalities with rare side effects also observed in some patients.(Alizadeh et al., 2012)

Aspirin conjugated with nanoparticles appeared as a remarkable drug in cancer like colorectal cancer drug and its beneficial and efficient performance in colorectal cancer with less cardiovascular disorders and reduced other toxicity. (Desai et al., 2019) Folic acid, aspirin, and calcium azoxymethane combination have proven to be very influential and effective drugs in treating colorectal cancer. (Chaudhary et al., 2011) Celecoxib is another nano-based particle that plays role in treating colorectal cancer but its terms and conditions vary with less cardiotoxicity.(Margulis-Goshen et al., 2011) Curcumin is a nanomaterial that plays a role in treating intestinal cancer ( Large and small bowel cancer ) but it has complications related to less absorption, and poor solubility (M. Wu et al., 2019)  Some researchers observed that the working

ability of curcumin can be improved by its conjugation with polymeric nanoparticles minimize the poor solubility effect and minimize the number of tumors (Zubair et al., 2017) Various types of nano enzymes that include liposome, nanoshells, carbon tubes, dendrimers, polymeric nanoparticles that are specially developed to shift anti polyp agents like siRNA, chemo-modulator, antiangiogenic mediators, etc. (Reshmitha et al., 2021) The use of nanotechnology in treating cancer proves to be very revolutionized and efficient.(Kriplani & Guarve, 2022) Many miRNA-based nanoparticles are AuNPs, Quantum dots, and silver nanoparticles, which are used to detect colorectal cancer.(Girigoswami & Girigoswami, 2021) . Nanoparticles in polyps need long time diagnosis and treatment in cancer cases. The connection between gold nanoparticles and their biodistribution plays an essential role in managing colorectal cancer.(Gmeiner & Ghosh, 2014) Silver-based nanoparticles provide powerful evidence in colorectal therapeutics. ROS and oxidative stress both are the reasons for silver-based nanoparticles' cytotoxicity, destroying the protein structure lipids structure, and DNA mutations.(Barabadi et al., 2020)

**Discussion:**

Colorectal cancer or any type of intestinal cancer including small or large bowel cancer is one of the most common causes of death due to cancer in the whole world. The utility of nanotechnology in cancer therapeutics is an emerging field and miraculously effective in the battle with cancer. Nanoenzymes are nanoparticles or nanocarriers artificially synthesized and prove very efficient in treating cancer. In recent eras, there is so much extension about the use of nanotechnology or nanoparticles in cancer theranostics. Nanomedicines have a remarkable role in colorectal cancer treatment. Nanoenzymes enable medicinal drugs or therapies from a unidirectional mode of action to multiple modes of action which is very effective in cancer treatment, especially in the colorectal case. Scientists are much encouraged to see the role of nanotechnology including nano enzymes

or nanoparticles in cancer and they are hopeful that one day this curse will not be as fatal and risky as it is now. Due to the nanoparticle's tiny size, it enters cells in a very adequate manner and forms a nano complex to prevent nuclear degradation and provide a fortunate entrance in tumor sites and prevent polyps from invading. Despite all challenges and trials one day nanotechnology including nano enzymes will provide 100% efficacy in colorectal cancer.

**REFERENCE:**

Abdul Khalek, F. J., Gallicano, G. I., and L. Mishra, 2010. Colon cancer stem cells. *Gastrointestinal Cancer Research: GCR*, *Suppl 1*, S16-23.

Ahles, T. A., Root, J. C., and E. L. Ryan, 2012. Cancer- and Cancer Treatment–Associated Cognitive Change: An Update on the State of the Science. *Journal of Clinical Oncology*, *30*(30), 3675–3686. https://doi.org/10.1200/JCO.2012.43.0116

Ahles, T. A., Root, J. C., and E.L. Ryan, 2012. Cancer-and cancer treatment–associated cognitive change: an update on the state of the science. *Journal of Clinical Oncology*, *30*(30), 3675.

Alizadeh, A. M., Khaniki, M., Azizian, S., Mohaghgheghi, M. A., Sadeghizadeh, M., and F. Najafi, 2012. Chemoprevention of azoxymethane-initiated colon cancer in the rat by using a novel polymeric nanocarrier–curcumin. *European Journal of Pharmacology*, *689*(1), 226–232. https://doi.org/10.1016/j.ejphar.2012.06.016

Allocati, N., Masulli, M., Alexeyev, M. F., and C. Di Ilio, 2013. Escherichia coli in Europe: An Overview. *International Journal of Environmental Research and Public Health*, *10*(12), Article 12. https://doi.org/10.3390/ijerph10126235

Amieva, M., and R.M. Peek, 2016. Pathobiology of Helicobacter pylori–Induced Gastric Cancer. *Gastroenterology*, *150*(1), 64–78. https://doi.org/10.1053/j.gastro.2015.09.004

Barabadi, H., Vahidi, H., Damavandi Kamali, K., Rashedi, M., Hosseini, O., Golnaraghi Ghomi, A. R., and M. Saravanan, 2020. Emerging Theranostic Silver Nanomaterials to Combat Colorectal Cancer: A Systematic Review. *Journal of Cluster Science*, *31*(2), 311–321. https://doi.org/10.1007/s10876-019-01668.

Bi, W. L., Hosny, A., Schabath, M. B., Giger, M. L., Birkbak, N. J., Mehrtash, A., Allison, T., Arnaout, O., Abbosh, C., Dunn, I. F., Mak, R. H., Tamimi, R. M., Tempany, C. M., Swanton, C., Hoffmann, U., Schwartz, L. H., Gillies, R. J., Huang, R. Y., and H. J.w. L. Aerts, 2019. Artificial intelligence in cancer imaging: Clinical challenges and applications. *CA: A Cancer Journal for Clinicians*, *69*(2), 127–157. https://doi.org/10.3322/caac.21552

Boellaard, R. 2018. *Quantitative oncology molecular analysis suite: ACCURATE*. Soc Nuclear Med.

Chaudhary, A., Sutaria, D., Huang, Y., Wang, J., and S. Prabhu, 2011. Chemoprevention of Colon Cancer in a Rat Carcinogenesis Model Using a Novel Nanotechnology-Based Combined Treatment System. *Cancer Prevention Research*, *4*(10), 1655–1664. https://doi.org/10.1158/1940-6207.CAPR-11-0129

Chen, C., Chen, L., Lin, L., Jin, D., Du, Y., and J. Lyu, 2021. Research progress on gut microbiota in patients with gastric cancer, esophageal cancer, and small intestine cancer. *Applied Microbiology and Biotechnology*, *105*(11), 4415-4425.

Cisterna, B. A., Kamaly, N., Choi, W. I., Tavakkoli, A., Farokhzad, O. C., and C. Vilos, 2016. Targeted nanoparticles for colorectal cancer. *Nanomedicine*, *11*(18), 2443–2456. https://doi.org/10.2217/nnm-2016-0194

Desai, P., Ann, D., Wang, J., and S. Prabhu, 2019. Pancreatic Cancer: Recent Advances in Nanoformulation-Based Therapies. *Critical Reviews&trade; in Therapeutic Drug Carrier Systems*, *36*(1). https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2018025459

Desai, P., Thumma, N. J., Wagh, P. R., Zhan, S., Ann, D., Wang, J., and S. Prabhu, 2020. Cancer Chemoprevention Using Nanotechnology-Based Approaches. *Frontiers in Pharmacology*, *11*. https://www.frontiersin.org/articles/10.3389/fphar.2020.00323

Feng, R.-M., Zong, Y.-N., Cao, S.-M., and Xu, R.-H. 2019. Current cancer situation in China: Good or bad news from the 2018 Global Cancer Statistics? *Cancer Communications*, *39*(1), 22. https://doi.org/10.1186/s40880-019-0368-6

Fokong, S., Theek, B., Wu, Z., Koczera, P., Appold, L., Jorge, S., Resch-Genger, U., van Zandvoort, M., Storm, G., Kiessling, F., and T. Lammers, 2012. Image-guided, targeted and triggered drug delivery to tumors using polymer-based microbubbles. *Journal of Controlled Release*, *163*(1), 75–81. https://doi.org/10.1016/j.jconrel.2012.05.007

Gill, S. S., Heuman, D. M., and A.A. Mihas, 2001. Small Intestinal Neoplasms. *Journal of Clinical Gastroenterology*, *33*(4), 267.

Girigoswami, K., and A. Girigoswami, 2021. A Review on the Role of Nanosensors in Detecting Cellular miRNA Expression in Colorectal Cancer. *Endocrine, Metabolic & Immune Disorders - Drug Targets(Formerly Current Drug Targets - Immune, Endocrine & Metabolic Disorders)*, *21*(1), 12–26. https://doi.org/10.2174/1871530320666200515115723

Gmeiner, W. H., and S. Ghosh, 2014. Nanotechnology for cancer treatment. *Nanotechnology Reviews*, *3*(2), 111–122. https://doi.org/10.1515/ntrev-2013-0013

Gunasekera, U. A., Pankhurst, Q. A., and M. Douek, 2009. Imaging applications of nanotechnology in cancer. *Targeted Oncology*, *4*(3), 169–181. https://doi.org/10.1007/s11523-009-0118-9

Ho, W. J., Jaffee, E. M., and L. Zheng, 2020. The tumour microenvironment in pancreatic cancer—Clinical challenges and opportunities. *Nature Reviews Clinical Oncology*, *17*(9), Article 9. https://doi.org/10.1038/s41571-020-0363-5

Huang, S., Yang, J., Fong, S., and Q. Zhao, 2020. Artificial intelligence in cancer diagnosis and prognosis: Opportunities and challenges. *Cancer Letters*, *471*, 61–71. https://doi.org/10.1016/j.canlet.2019.12.007

Iacopetta, B., 2002. Are there two sides to colorectal cancer? *International Journal of Cancer*, *101*(5), 403–408. https://doi.org/10.1002/ijc.10635

Kotov, N. A., 2010. Inorganic Nanoparticles as Protein Mimics. *Science*, *330*(6001), 188–189. https://doi.org/10.1126/science.1190094

Kriplani, P., and K. Guarve, 2022. Nanotechnology a boon for colorectal cancer treatment. *Recent Patents on Anti-Cancer Drug Discovery*. https://doi.org/10.2174/1574892817666221011094619

Knudsen, M. D., Kyrø, C., Olsen, A., Dragsted, L. O., Skeie, G., Lund, E., and R. Landberg, 2014. Self-reported whole-grain intake and plasma alkylresorcinol concentrations in combination in relation to the incidence of colorectal cancer. *American journal of epidemiology*, *179*(10), 1188-1196.

Liang, M., and X.Yan, 2019. Nanozymes: From New Concepts, Mechanisms, and Standards to Applications. *Accounts of Chemical Research*, *52*(8), 2190–2200. https://doi.org/10.1021/acs.accounts.9b00140

Liu, Q., Zhang, A., Wang, R., Zhang, Q., and D. Cui, 2021. A Review on Metal- and Metal Oxide-Based Nanozymes: Properties, Mechanisms, and Applications. *Nano-Micro Letters*, *13*(1), 154. https://doi.org/10.1007/s40820-021-00674-8

Lyu, Y., and P. Scrimin, 2021. Mimicking Enzymes: The quest for powerful catalysts from simple molecules to nanozymes. *ACS Catalysis*, *11*(18), 11501-11509.

Ma, Q., Liu, Y., Zhu, H., Zhang, L., and X. Liao, 2021. Nanozymes in Tumor Theranostics. *Frontiers in Oncology*, *11*. https://www.frontiersin.org/articles/10.3389/fonc.2021.666017

Margulis-Goshen, K., Weitman, M., Major, D. T., and S. Magdassi, 2011. Inhibition of crystallization and growth of celecoxib nanoparticles formed from volatile microemulsions. *Journal of Pharmaceutical Sciences*, *100*(10), 4390–4400. https://doi.org/10.1002/jps.22623

Morson, B. C., and  H. J. R . Bussey,1970. Predisposing causes of intestinal cancer. *Current*

*Problems in Surgery*, *7*(2), 1–50. https://doi.org/10.1016/S0011-3840(70)80006-5

Neugut, A. I., Marvin, M. R., Rella, V. A., and J. A. Chabot, 1997. An overview of

adenocarcinoma of the small intestine. *ONCOLOGY-WILLISTON PARK THEN*

*HUNTINGTON-*, *11*, 428-431.

Pan, S. Y., and H. Morrison, (2011). Epidemiology of cancer of the small intestine. *World*

*journal of gastrointestinal oncology*, *3*(3), 33.

Reshmitha, T. R., Shini, V. S., and P. Nisha, 2021. Nanotechnology Approaches for Colorectal

Cancer Diagnosis and Therapy. In N. K. Vishvakarma, G. P. Nagaraju, & D. Shukla (Eds.),

*Colon Cancer Diagnosis and Therapy: Volume 2* (pp. 171–186). Springer International

Publishing. https://doi.org/10.1007/978-3-030-64668-4_8

Siravegna, G., Marsoni, S., Siena, S., and A. Bardelli, 2017. Integrating liquid biopsies into the

management of cancer. *Nature Reviews Clinical Oncology*, *14*(9), Article 9.

https://doi.org/10.1038/nrclinonc.2017.14

Sterner, R. C., and R. M.Sterner, 2021. CAR-T cell therapy: Current limitations and potential

strategies. *Blood Cancer Journal*, *11*(4), Article 4. https://doi.org/10.1038/s41408-021-

00459-7

Tebbutt, N. C., Norman, A. R., Cunningham, D., Hill, M. E., Tait, D., Oates, J., Livingston, S.,

and J. Andreyev, 2003. Intestinal complications after chemotherapy for patients with

unresected primary colorectal cancer and synchronous metastases. *Gut*, *52*(4), 568–573.

Testa, U., Pelosi, E., and G. Castelli, 2018. Colorectal Cancer: Genetic Abnormalities, Tumor Progression, Tumor Heterogeneity, Clonal Evolution and Tumor-Initiating Cells. *Medical Sciences*, *6*(2), Article 2. https://doi.org/10.3390/medsci6020031

Vyas, D., Castro, P., Saadeh, Y., and A. Vyas, 2014. The Role of Nanotechnology in Gastrointestinal Cancer. *Journal of Biomedical Nanotechnology*, *10*(11), 3204–3218. https://doi.org/10.1166/jbn.2014.1816

Wu, J., Wang, X., Wang, Q., Lou, Z., Li, S., Zhu, Y., Qin, L., and H. Wei, 2019. Nanomaterials with enzyme-like characteristics (nanozymes): Next-generation artificial enzymes (II). *Chemical Society Reviews*, *48*(4), 1004–1076. https://doi.org/10.1039/C8CS00457A

Wu, M., Wang, G., Hu, W., Yao, Y., and X.-F. Yu,. 2019. Emerging roles and therapeutic value of exosomes in cancer metastasis. *Molecular Cancer*, *18*(1), 53. https://doi.org/10.1186/s12943-019-0964-8

Younis, N. K., Roumieh, R., Bassil, E. P., Ghoubaira, J. A., Kobeissy, F., and A.H. Eid, 2022. Nanoparticles: Attractive tools to treat colorectal cancer. *Seminars in Cancer Biology*, *86*, 1–13. https://doi.org/10.1016/j.semcancer.2022.08.006

Zeino, Z., Sisson, G., and I. Bjarnason, 2010. Adverse effects of drugs on small intestine and colon. *Best Practice & Research Clinical Gastroenterology*, *24*(2), 133–141. https://doi.org/10.1016/j.bpg.2010.02.008

Zhang, L.-N., Deng, H.-H., Lin, F.-L., Xu, X.-W., Weng, S.-H., Liu, A.-L., Lin, X.-H., Xia, X.-H., and W. Chen, 2014. In Situ Growth of Porous Platinum Nanoparticles on Graphene Oxide for Colorimetric Detection of Cancer Cells. *Analytical Chemistry*, *86*(5), 2711–2718. https://doi.org/10.1021/ac404104j

Zhang, R., Zhou, Y., Yan, X., and K. Fan, 2019. Advances in chiral nanozymes: A review. *Microchimica Acta*, *186*(12), 782. https://doi.org/10.1007/s00604-019-3922-7

Zubair, H., Azim, S., Ahmad, A., Khan, M. A., Patel, G. K., Singh, S., and A.P. Singh, 2017. Cancer Chemoprevention by Phytochemicals: Nature's Healing Touch. *Molecules*, *22*(3), Article 3. https://doi.org/10.3390/molecules22030395

Zugazagoitia, J., Guedes, C., Ponce, S., Ferrer, I., Molina-Pinelo, S., and L. Paz-Ares, 2016. Current Challenges in Cancer Treatment. *Clinical Therapeutics*, *38*(7), 1551–1566. https://doi.org/10.1016/j.clinthera.2016.03.026


Zuo, Z., Ji, S., He, L., Zhang, Y., Peng, Z., & Han, J. (2020). LncRNA TTN-AS1/miR-134-5p/PAK3 axis regulates the radiosensitivity of human large intestine cancer cells through the P21 pathway and AKT/GSK-3β/β-catenin pathway. *Cell Biology International*, *44*(11), 2284-2292.