**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 16780**

**Columns: EDITORIAL**

**Gastrointestinal cancers in the era of theranostics: Updates and future perspectives**

Ghosn M *et al.* GI cancers in the era of theranostics

Marwan Ghosn, Hampig Raphael Kourie, Samer Tabchi

**Marwan Ghosn, Hampig Raphael Kourie, Samer Tabchi,** Hematology-oncology department, Faculty of Medicine, Saint Joseph University, Beirut 1104-2020, Lebanon

**Author contributions:**Ghosn M initiated the review; Kourie HR and Tabchi S performed the review and wrote and analyzed the data.

**Conflict-of-interest:** The authors confirm that they do not have any conflict of interest.

**Open-Access:** This article is an open-access article, which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Marwan Ghosn, MD,** Department of Oncology, Faculty of Medicine, Saint Joseph University, Alfred Naccache Street, PO Box 166830, Beirut 1104-2020,Lebanon. mghosn.hdf@usj.edu.lb

**Telephone:** +961-3-226842

**Fax**: +961-1-613397

**Received:** January 29, 2015

**Peer-review started:** January 29, 2015

**First decision:** March 10, 2015

**Revised:** March 22, 2015

**Accepted:** May 2, 2015

**Article in press:**

**Published online:**

**Abstract**

Theranostics is one of the practical aspects of personalized medicine. Basically, this concept was designed to describe a material combining diagnosis, treatment and follow up of a disease. Actually, it evolved and included molecular targeting and nanotechnologies that incorporate both diagnosis and therapeutics. In this editorial, we are presenting briefly the concept and evolution of theranostics, highlighting many applications of theranostics in daily practice and discussing future perspectives and aspects of this model in gastro-intestincal cancers.

**Key words:** Theranostics; Gastrointestinal cancer; Nanoparticles; Nanotherarostics; Molecular targeting

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This editorial presents briefly the concept and evolution of theranostics. It describes the actual use of this treatment modality in GI cancer going from the success story of theranostics in pancreatic neuroendocrine tumors to the promising results in gastric and colon cancer. Future perspectives of theranostics in GI cancers in nanotechnology and biomarkers fields are also reported in the end of this editorial.

Ghosn M, Kourie HR, Tabchi S. Gastrointestinal cancers in the era of theranostics: Updates and future perspectives. *World J Gastroenterol* 2015; In press

**THERANOSTICS: CONCEPT AND EVOLUTION**

The Edwin Smith papyrus, dating back to 3000 B.C., describes cancer as an entity that is beyond the reach of any cure[1]. Science has taken us through immeasurable lengths since that categorical statement was drafted. Our present day has witnessed an era of unprecedented advancement in the field of cancer therapeutics.

The dawn of the twentieth century saw the “unintentional” birth of personalized medicine when Beatson first started using oophorectomy as a treatment for breast cancer[2]. Since then, bringing about a true state of precision cancer care, in every sense of the word, has become the holy grail of modern physicians and researchers. The term “theranostics” is simply a by-product of the pharmaceutical industry, in its effort to establish diagnostic tests that also possess the ability to affect the treatment of a certain cancer[3]. Effectively, the need for validated predictive biomarkers was essential in order to transform cancer care into a precise, patient-centred science, in contrast to a crude, reactive, population-based, one size fits all discipline. HER-2 over-expression by breast cancer cells is perhaps the example that portrays a predictive biomarker the best, especially since the approval of Trastuzumab in 1998 drastically changed the treatment paradigm for patients with breast cancer[4,5]. No less can be said about BRAF V600E mutations in melanoma, KRAS/NRAS mutations in colorectal carcinoma, EGFR mutations, ALK gene rearrangement and most recently ROS-1 mutations in Non-Small Cell Lung Carcinoma and many other validated biomarkers with palpable results in different areas of clinical oncology[6-9].

While the definition of theranostics certainly applies to predictive biomarkers commonly used in clinical practice, it is still an evolving concept that encompasses many facades for managing malignant disease. Present and near-future perspectives are looking into theranostic nano-medicine as a tool for achieving a more refined personal medicine, better tailored to the need of each and every patient. This emerging concept would have us probe deeper into the realm of nanoparticles (NP), synthetic materials with dimensions ranging from tens to hundreds of nanometers, which have gained increasing popularity in the past decade for their efficacy in drug delivery with reduced systemic toxicity, such is the case of albumin bound paclitaxel nanoparticles (Abraxane®)[10]. In contrast, some experimental models of these NP, considered “smart” NP, have no clinical application beyond animal models to date, but the results envisioned are well within grasp for implementation in current practice. “Activatable” NP would respond to changes in the microenvironment to exert their therapeutic or diagnostic mechanism. Therefore, NP could be selective for a certain tumor environment, such as acidic pH resulting from tumor hypoxia and consequent lactic acid production, in order to subsequently release their content[11]. Other forms of NP would use protease that are known to be up-regulated by tumor or irradiation with a predetermined wavelength of light to trigger them into action[12-13]. This creates an opening for the perfection of multifunctional NP with both diagnostic and therapeutic applications simultaneously.

Theranostic NP and their impact on clinical oncology will certainly keep moving forward in the coming years as the need for less invasive and more specific therapeutic alternatives is growing. Our current ambition is aimed at securing NP that would identify the malignant clone and treat it through optimal drug delivery. However, a more futuristic ambition would be to create what is referred to as “nanobots”, as these “artificial cells” would continuously circulate in the host’s system and activate theranositcs at the earliest disease state.

**THERANOSTICS IN GI CANCERS**

The success of radiolabeled Somatostatine analogs in the diagnosis and the treatment of gastrointestinal and pancreatic neuroendocrine tumors widely opened the doors for more trials and protocols based on the Theranostic concept in GI tumors.

***Success story: Theranostics in Gastrointestinal and pancreatic neuroendocrine tumors***

Neuroendocrine tumors originate from different neuroendocrine cells distributed in the human organism; these cells contain granules secreting amines and peptides[14]. The most frequent sites of these tumors are gastro-intestinal and bronco-pulmonary tracts[15]. NETs are usually considered with favorable prognosis with a five-year survival reaching the 80%[16]. NETs have many specific and particular characteristics including the presence of peptide receptors and transporters at the cell membrane and the neuroamine uptake mechanisms, which lead to the clinical implication of specific radiolabeled ligands for imaging and therapy in these tumors. Somatostatine receptors are expressed in a high percentage of NETs and they became the ideal entity to be targeted in these tumors. Somatostatine targeting was incriminated in diagnostic and therapeutic level in NET tumors, becoming a model in GI theranostics.

Somatostatine receptor imaging is based on the use of PET or SPECT (scintigraphy) as whole-body techniques; many tracers are included in the panel used for imaging with different degrees of sensitivity and specificity. Octreosan using 111In-pentetreotide was considered for many years the gold standard but actually new more reliable tracers are showing a better performance in visualizing NET tumors. Besides the imaging utility, combining somatostatine analogues with therapeutic beta emitters (lutetuin-177 and yttrium-90) is considered an efficient therapeutic option for patient with metastasized and unresectable NETs. Targeting the same marker in imaging and therapeutic in NET, the somatostatine receptors, was considered the first success in the era of theranostics in GI tumors[17].

***Her2neu in gastric cancer and KRAS in colon cancer***

In GI cancers, only two molecular mutations are approved as predictive therapeutic targets in daily practice. The Her2neu is a positive predictive factor in advanced gastric cancer and KRAS is a negative predictive factor in metastatic colon cancer.

The overexpression of Her2neu in advanced gastric and gastro-esophageal junction cancer is considered a positive predictive factor to the response to Trastuzumab , a monoclonal antibody against human epidermal growth factor receptor 2 (HER2; also known as ERBB2) . The TOGA trial showed an overall survival of 13.8 mo in patients with Her2neu overexpression, when treated with trastuzumab associated to chemotherapy in first line treatment, while the overall survival doesn’t exceed one year in the population not receiving trastuzumab[18].

KRAS mutation is a negative predictive factor for the use of Cetuximab , an anti-EGFR, in metastatic colon cancer . KRAS mutated patients will not benefit from Cetuximab as much as the patients with wild type KRAS, these patients will preferentially be treated with bevacizumab[19].

**FUTURE PERSPECTIVES OF THERANOSTICS IN GI CANCERS**

***Nanotheranostics***

After the progress in nanotechnology in the last decade, many trials were launched aiming to integrate this technology in theranostics under the name of “nanotheranostics”. The introduction of this new technology in health care routine needs many practical steps in the long way of concretization and daily application. Many nanoparticles were been studying in this domain; gold-based nanoparticles, magnetic nanomaterials and polymeric nanomaterials are the most widely tested associated sometimes to chemotherapeutical agents. These nanotechnologies are being applied first *in vitro*, and subsequently *in vivo* with many positive results (Table 1).

The association of chemotherapeutical agents with nanoparticles avoid the drug degradation, allow higher dose of antitumor agents with less toxicities and a higher penetrance to malignant tissue with more specificity.

***Gastro-esophageal cancer***

Many combinations based on nanoparticles are being investigated in gastro-esophageal cancer; some nanoplatforms are targeting metaplasia, the precursor of gastric and esophageal adenocarcinoma[20]. The type of nanoparticles studied in theranostics of gastro-esophageal cancer are polypeptide NP[21], magnetic NP of iron[22], triblock copolymer NP[23]. All these NP are not included in clinical trial or for commercial use.

***Pancreatic cancer***

Pancreatic cancers are known to have one of the poorest prognosis in GI cancers. Treatment of this cancer is limited by resistance of cancer cells to chemotherapy and impaired drug penetration due to the dense stroma formed around the tumor. Nano-sized cytotoxic agents have showed increased drug efficacy, a concrete example is approval of nab-paclitaxel as a therapeutic option in metastatic pancreatic cancer[24].

Different categories of nanoparticles are being investigated in pancreatic cancer; the iron oxide is one the subtypes having promising results in this type of cancer[25]. Many studies are evaluating the different modalities of use of iron oxide nanoparticules as theranostics agents: Iron oxide nanoparticules as vehicule of chemotherapy[26] or gold coated iron oxide nanoparticules[27]. All these studies showed a promising potential of iron oxide nanothenostics in pancreatic cancer. More investigations should be carried out to optimize in order to optimize the parameters and to understand the detailed mechanisms of action of these nanoparticles.

The national cancer institute alliance for nanotechnology in cancer launched a new project to develop a multifunctional theranostic nanoparticle platform that combines demonstrated imaging capability and receptor specificity of the nanoparticles with novel designs for tumor-targeted drug delivery in pancreatic cancer[28]. Rapid diagnosis and treatment using iron oxide theranostics may change the prognosis of pancreatic cancer in the next decade.

***Colorectal cancer***

Despite the major efforts and the important progress in the treatment of colorectal cancer after the use of targeted therapies, the metastatic colo-rectal cancer remains an incurable disease. The nanotheranostics will most probably bring a new hope and add a positive impact on the prognosis and evolution of this disease.

Different new nanoparticles are being designed worldwide to assure a new way of delivering drug with higher doses, less tocixity and more specificity in colo-rectal cancer. As in pancreatic and gastro-esophageal cancer, many NP specific for colo-rectal cancer as polymeric nanosphere[29], micelle particles[30], metal semi-conductor nanoparticles[31] and gold nanoparticles are being elaborated[32] .

One of the ideal examples for theranostics in colon cancer is designed by Soon *et al*[33] who developed a nanoparticle containing a magnetic material core associated with organic fluorescent material and an antibody (Cetuximab ) for the specific diagnostic and treatement of these tumors.

**NEW MOLECULAR TARGETS**

The stratification of cancers into their molecular mutations, alterations or overexpression remains an important step in personalized medicine, before finding the accurate targeted therapy for each mutation. Nowadays, an important number of oncogenic driver alterations implicated in carcinogenesis are detected in lung adenocarcinoma and in breast cancer, but only few targeted therapies are approved in these two cancers. Many new targets are being identified in gastro-intestinal cancers and will probably be incriminated in future theranostics projects.

Next to Her2neu overexpression, MET and FGFR2 overexpression are considered potential therapeutic targets in this type of cancer in gastric cancer due to their role as oncogenic driver alterations. STAT3 seems to be a potential future target in the treatment of pancreatic cancer next to P53 and SMAD4. All these targets and many others will help the development of new treatment modalities based on theranostics[34].

**REFERENCES**

1 **Hajdu SI**. A note from history: landmarks in history of cancer, part 1. *Cancer* 2011; **117**: 1097-1102 [PMID: 20960499 DOI: 10.1002/cncr.25553]

2 **Love RR**, Philips J. Oophorectomy for breast cancer: history revisited. *J Natl Cancer Inst* 2002; **94**: 1433-1434 [PMID: 12359852 DOI: 10.1093/jnci/94.19]

3 **Sumer B**, Gao J. Theranostic nanomedicine for cancer. *Nanomedicine* (Lond) 2008; **3**: 137-140 [PMID: 18373419 DOI: 10.2217/17435889.3.2.137]

4 **Moja L**, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012; **4**: CD006243 [PMID: 22513938 DOI: 10.1002/14651858.CD006243.pub2]

5 **Balduzzi S**, Mantarro S, Guarneri V, Tagliabue L, Pistotti V, Moja L, D'Amico R. Trastuzumab-containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev* 2014; **6**: CD006242 [PMID: 24919460 DOI: 10.1002/14651858.CD006242.pub2]

6 **Hao M**, Song F, Du X, Wang G, Yang Y, Chen K, Yang J. Advances in targeted therapy for unresectable melanoma: new drugs and combinations. *Cancer Lett* 2015; **359**: 1-8 [PMID: 25578781 DOI: 10.1016/j.canlet.2014.12.050]

7 **Hendifar A**, Tan CR, Annamalai A, Tuli R. Biomarker-driven EGFR therapy improves outcomes in patients with metastatic colorectal cancer. *Expert Rev Anticancer Ther* 2014; **14**: 1051-1061 [PMID: 24898788 DOI: 10.1586/14737140.2014.922881]

8 **Shaw AT**, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, Riely GJ, Varella-Garcia M, Shapiro GI, Costa DB, Doebele RC, Le LP, Zheng Z, Tan W, Stephenson P, Shreeve SM, Tye LM, Christensen JG, Wilner KD, Clark JW, Iafrate AJ. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2014; **371**: 1963-1971 [PMID: 25264305 DOI: 10.1056/NEJMoa1406766]

9 **Stinchcombe TE**. Recent advances in the treatment of non-small cell and small cell lung cancer. *F1000Prime Rep* 2014; **6**: 117 [PMID: 25580271 DOI: 10.12703/P6-117]

10 **Desai N,** Trieu V, Yao Z, Louie L, Ci S, Yang A, Tao C, De T, Beals B, Dykes D, Noker P, Yao R, Labao E, Hawkins M, Soon-Shiong P. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitax- el. *Clin Cancer Res* 2006; **12**: 1317-1324 [DOI: 10.1158/1078-0432.CCR-05-1634]

11 **Devalapally H**, Shenoy D, Little S, Langer R, Amiji M. Poly(ethylene oxide)-modified poly(beta-amino ester) nanoparticles as a pH-sensitive system for tumor-targeted delivery of hydrophobic drugs: part 3. Therapeutic efficacy and safety studies in ovarian cancer xenograft model. *Cancer Chemother Pharmacol* 2007; **59**: 477-484 [PMID: 16862429 DOI: 10.1007/s00280-006-0287-5]

12 **Harris TJ**, von Maltzahn G, Derfus AM, Ruoslahti E, Bhatia SN. Proteolytic actuation of nanoparticle self-assembly. *Angew Chem Int Ed Engl* 2006; **45**: 3161-3165 [PMID: 16642514 DOI: 10.1002/anie.200600259]

13 **McCarthy JR**, Perez JM, Brückner C, Weissleder R. Polymeric nanoparticle preparation that eradicates tumors. *Nano Lett* 2005; **5**: 2552-2556 [PMID: 16351214 DOI: 10.1021/nl0519229]

14 **Koopmans KP,** Neels ON, Kema IP. "Molecular imaging in neuroendocrine tumors: molecular uptake mechanisms and clinical results." *Crit Rev Oncol Hematol* 2009; **71**: 199–213 [DOI: 10.1016/j.critrevonc.2009.02.009]

15 **Rufini M,** Calcagni L, Baum RP. Imaging of neuroendocrine tumors. *Semin Nucl Med* 2006; **36**: 228–247 [PMID: 16762613 DOI: 10.1053/j.semnuclmed.2006.03.007]

16 **Pape UF,** Berndt U, M¨uller-Nordhorn J. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. *Endocrine-Related Cancer* 2008; **15**: 1083–1097 [DOI: 10.1677/ERC-08-0017]

17 **Wang L**, Tang K, Zhang Q, Li H, Wen Z, Zhang H, Zhang H. Somatostatin receptor-based molecular imaging and therapy for neuroendocrine tumors. *Biomed Res Int* 2013; **2013**: 102819 [PMID: 24106690 DOI: 10.1155/2013/102819]

18 **Bang YJ,** Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [DOI: 10.1016/S0140-6736(10)61121-X]

19 **Van Cutsem E,** Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Tejpar S, Schlichting M, Zubel A, Celik I, Rougier P, Ciardiello F. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011; **29**: 2011-2019 [DOI: 10.1200/JCO.2010.33.5091]

20 **Xian W,** McKeon F, Vincent M, Crum C, Ho KY. Methods and reagents for detection and treatment of esophageal metaplasia. Available from: URL: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2012044992&recNum=107&docAn=US2011054323&queryString=microRNA&maxRec=4066

21 **Tung CH,** Abd-Elgaliel WR. Protease degradable polypeptides and uses thereof. Available from: URL: http://www.google.com/patents/WO2012075241A3?cl=en

22 **Zeng Q,** Baker I. Iron/iron oxide nanoparticle and use thereof. Available from: URL: http://www.google.com/patents/WO2012036978A1?cl=en

23 **El-Sayed MEH,** Yuksel Durmaz Y. Polymeric nanoparticles for ultrasound imaging and therapy. Available from: URL: http://www.google.com/patents/WO2013055791A1?cl=en

24 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]

25 **Malekigorji M,** Curtis ADM, Hoskins C. The Use of Iron Oxide Nanoparticles for Pancreatic Cancer Therapy. *J Nanomed Res* 2004; **1**: 4 [DOI: 10.15406/jnmr.2014.01.0000426]

26 **Kievit FM**, Zhang M. Surface engineering of iron oxide nanoparticles for targeted cancer therapy. *Acc Chem Res* 2011; **44**: 853-862 [PMID: 21528865 DOI: 10.1021/ar2000277]

27 **Guo Y**, Zhang Z, Kim DH, Li W, Nicolai J, Procissi D, Huan Y, Han G, Omary RA, Larson AC. Photothermal ablation of pancreatic cancer cells with hybrid iron-oxide core gold-shell nanoparticles. *Int J Nanomedicine* 2013; **8**: 3437-3446 [PMID: 24039426 DOI: 10.2147/IJN.S47585]

28 **Yang L,** Mao H. Theranostic Nanoparticles for Targeted Treatment of Pancreatic Cancer. National cancer institute alliance for nanotechnology in cancer. Available from: URL: http: //nano.cancer.gov/action/programs/platforms/emorysm.asp

29 **Iyer KL,** Evans CW, Clemons TD, Fitzgerald M, Dunlop SA, Luzinov I, Zdyrko B. Multifunctional nanoparticles. Available from: URL: <http://www.google.com/patents/WO2012075533A1?cl=en>

30 **Zhao Y.** Nanoparticles and nanoparticle compositions. Available from: URL: http://www.google.ee/patents/WO2011130114A1?cl=et

31 **Bayford RH,** Roitt IM, Rademacher TW, Demosthenous A, Iles RK. Detection of cancer. Available from: URL: http://www.google.ee/patents/ WO2010052503?cl=et

32 **Liu W,** Hainfeld JF. 5 NM nickel-NTA-gold nanoparticles. Available from: URL: <http://www.freepatentsonline.com/y2012/0244075.html>

33 **Soon JE,** Yuk CK, Seok CY, Jong YT, Hong AC, Tae KK, Hyun CZ, Young RJ, Keun CB, Jeong CE, Chul YG. Nanoparticles conjugates with a cetuximab antibody for diagnosis of colon cancer, and a method for preparing the same. KR100830889 (2008).

34 **Liu YJ,** Shen D, Yin X, Gavine P, Zhang T, Su X, Zhan P, Xu Y, Lv J, Qian J, Liu C, Sun Y, Qian Z, Zhang J, Gu Y, Ni X. HER2, MET and FGFR2 oncogenic driver alterations define distinct molecular segments for targeted therapies in gastric carcinoma. *Br J Cancer* 2014; **110**: 1169-1178 [DOI: 10.1038/bjc.2014.61]

**P-Reviewer:** Hummel R, Yan M **S-Editor:** Qi Y **L-Editor: E-Editor:**

# Table 1 Approved molecular theranostics and nanoparticles in gastrointestinal cancers

1PNET. NP: Nanoparticles.

|  |  |  |
| --- | --- | --- |
|  | **Molecular theranostics** | **Nanoparticles** |
| Gastric cancer | Her2neu | Polypeptide NP  Magnetic NP of iron  Triblock copolymer NP |
| Colon cancer | KRAS | Polymeric nanosphere Micelle particles,  Metal semi-conductor NP  Gold NP |
| Pancreas cancer | Somatostatine receptors1 | Iron oxide NP  Gold coated iron oxide NP |