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Recent advances in targeted therapy of colorectal cancer: impacts of monoclonal antibodies nanoconjugates

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Summary

Despite rapid advances in diagnostic and treatment approaches, the overall survival rate of cancer has not been improved. Colorectal cancer (CRC) is recognized as the third leading cause of neoplasm-related deaths worldwide, in large part due to its considerable metastasis and drug resistance. For developing new anticancer strategies, rapid progression of multimodal nanomedicines and nanoconjugates has provided promising treatment modalities for effective therapy of cancer. The limitations of cancer chemotherapy might be overcome through the use of such nanosized therapeutics, including nanoconjugates of monoclonal antibodies (mAbs) along with drugs and organic/inorganic nanoparticles. CRC cells express various molecular markers against which mAbs can be designed and used as targeting/therapeutic agents. This editorial highlights the importance of such targeted nanosystems against CRC.

Authors' Biosketch

Mostafa Akbarzadeh Khiavi M.Sc., is a Ph.D. candidate in medical genetics at Liver and Gastrointestinal Diseases Research Center (LGDRC) and Research Center for Pharmaceutical Nanotechnology (RCPN), under the mentorship of Prof. M.H. Somi and Prof. Y. Omidi, working on the development of advanced nanoformulated enzyme/antibody used for the targeted drug delivery. Presently, he is involved in projects for the delivery of targeted ribonuclease nano-enzyme by monoclonal antibody for solid tumor therapy.

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Colorectal cancer (CRC) ranks as the third most prevalent cancer globally and the second potent cause of cancer-associated deaths in developed countries.[1] Different strategies such as chemotherapy, surgery, radiation therapy, and immunotherapy, as well as nutritional-supplement therapy have been employed for CRC treatment.[2] However, these approaches are accompanied with certain pitfalls and restrictions such as bleeding, rash, nausea, diarrhea, neuropathy, hair loss, healthy cells damages, and decreased bioavailability of high molecular weight chemotherapeutic agents, as well as drug resistance.[3] Moreover, several parameters such as the lack of efficiency and selectivity in drug delivery systems, drug influx and efflux, metabolic alterations, drug sequestration or repossession, disruption of apoptotic pathways, and certain changes in signal transduction pathways, as well as activation of DNA repair mechanisms can lead to the development of drug resistance.[4] Regarding these limitations, the development of effective site-specific drug delivery systems are required to prevent the growth, progression, and spread of cancer, and to leave out all rapidly dividing cells.[5,6] In solid tumors such as CRC, the cancer cells for a permissive microenvironment (TME: tumor microenvironment),[7,8] within which they represent higher ability to overexpress the molecular markers and receptors including vascular

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endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), epithelial cell adhesion molecule (EpCAM), insulin-like growth factor 1 receptor (IGF-1R), death receptor (DR5), mucin 5AC (MUC5AC), alpha v beta 3 integrin (aVb3 integrin), Human epidermal growth factor receptor-2 (HER2/neu), and Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) on their cell membranes compared to normal cells. Therefore, the active targeting approaches would provide beneficial results in cancer therapy.[9-11] Following the activation of these transmembrane receptors, multiple intracellular signal transduction pathways are stimulated, which finally lead to cell proliferation, dedifferentiation, and inhibition of apoptosis, as well as the induction of neoangiogenesis.[12]

VEGF and EGFR are two key molecular markers and receptors in the growth and dissemination of tumors especially CRC.[13, 14] EGFR expression has been observed in almost 70% of human colorectal carcinomas [15] and VEGF is minimally expressed in approximately 50% of CRCs. However, these receptors have a comparatively lower expression in normal colonic mucosa and adenomas.[16] The VEGF and EGFR share common downstream signaling pathways. Moreover, the epidermal growth factor (EGF) has the potential to trigger the expression of VEGF.[17]

Regarding that VEGFR and EGFR play pivotal roles in tumor progression, invasion, and metastasis, their signaling pathways can be potential and feasible targets for pharmacologic intervention in solid tumors. Moreover, they have the great potency to be employed in targeted drug delivery systems against CRC.[18, 19]

Recently, interests have been focused on an important molecular marker namely DR5 as a target in cancer therapy.[20, 21] DR5 overexpression in CRCs has been substantiated in some studies.[22, 23] Specific bio-molecular approaches to CRC therapies provided considerable relevance in an attempt to find a more selective action in the last few years.[24] The present targeting moieties are categorized in two groups; the first one is monoclonal antibodies (mAbs), which bind to the ligand or the external domain of a receptor, and the second one is small-molecule tyrosine kinase (TK) inhibitors that recognize TK domain in the intracellular part of the receptor. These targeting molecules hinder the TK receptors-generated signaling pathways that are essential for the growth of tumor cells.[25] MAbs are favorable tools owing to their specific targeting and powerful anticancer functions and happen via several mechanisms.[10] Among mAbs, only cetuximab, bevacizumab, and panitumumab have been authenticated for CRC treatment in the USA; while many others are still undergoing clinical trials.[26, 27] Targeting mAbs affect tumor cells through multiple mechanisms. They can perturb tumors growth signaling pathways by altering the activation state of membrane-bound receptors or neutralizing cytokines that are essential for cellular growth and proliferation. Furthermore, the binding between the Fc portion of Abs and Fc receptor (FcR) present on immune effector cells takes part in an anti-tumor activity by stimulating antibody-dependant cell-mediated cytotoxicity (ADCC).[28]

MAbs display great ability to exclusively identify cancer cell-surface receptors.[29] Nevertheless, the applications of these biomolecules have been restricted due to some resistance (intrinsic or acquired) to the receptor inhibitors.[30, 31] For instance, studies have shown that anti-EGFR therapy has no beneficial effect on approximately 80% of unselected mCRCs, which indicates the prevalence of primary resistance to anti-EGFR therapy in CRC treatment.[32, 33]

To overcome these major complications, various forms of multidrug-resistant nano-based drugs have provided new opportunities due to their fast drug design, flexibility, and production based on genetic tumor profiles.[34-36] Investigators have unprecedentedly explored nanotechnology for synthesizing biodegradable nanoscale drug carriers with negligible side effects, which are able to specifically target tumor sites.[37] The goal of nanotechnology is to boost effective and reliable systems for precise diagnosis and anti-cancer therapy. Multifunctional diagnostic and therapeutic nanosystems (NSs) have been developed by arming NSs with various imaging probes, targeting agents [e.g., antibodies (Abs)/aptamers (Aps)], and enzymes.[13, 38] These targeted NSs are successfully being used for simultaneous detection and treatment of various cancers.[39, 40] Aps, as short length double/single-stranded DNA or RNA molecules, can bind to their specific biological targets (e.g., genes, peptides, proteins, and even cells) with high affinity. However, some problems of Aps such as less circulating half-life, renal filtration due to small size, and fast degradation by nucleases have to be solved before clinical applications.[41] In order to establish a targeting approach and to accomplish the aforementioned goal, bio-conjugation of nanoparticles (NPs) loaded with therapeutic agents by using mAb (Fig. 1) or their analogs have been considered both *in-vivo* and *in-vitro*.[42] Surface modification of NPs using specific ligand conjugation may eliminate nonspecific uptake of nanocarriers to tissues other than tumor ones.[13] These ligands have high specificity against receptors that are overexpressed on the surface of tumor cells, such as EGFR and VEGFR.[5, 43] Up to now, several mAbs and their nanoformulation by using liposomes, dendrimers, micelles, and polymeric, as well as inorganic NPs have been approved for clinical applications in CRCs (Table 1). It has been shown that the encapsulated celecoxib within the targeted liposome with mAbs has improved toxicity in EGFR-overexpressed cancer cells.[44] Furthermore, it has been demonstrated that targeted carbon nanotubes (CNTs) with cetuximab (EGFR-antibody) specifically binds to EGFR-expressing cells; besides, the cellular uptake of targeted CNTs were much higher than that of the negative control.[45]

Nanomedicine technology can provide different tools for developing new anticancer strategies and the

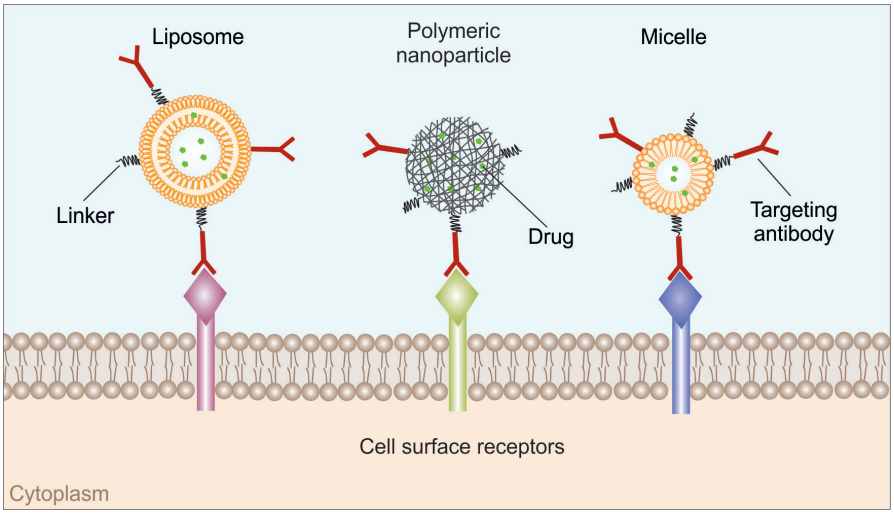

Fig. 1. Schematic illustration of monoclonal antibodies nanoconjugates.

Table 1. Monoclonal antibodies and their nanoformulations for colorectal cancer targeting

Name of mAb	Target	Formulation	Bioactives	Ref
Bevacizumab	VEGF	Mesoporous silica NPs	MiR-328	50
Cetuximab	EGFR	Magneto-fluorescent silica NPs (MFSN)	-	51
Panitumumab	EGFR	Platinum-Cored Apoferritin Nanocages	Oxaliplatin	52
Matuzumab	EGFR	Liposomes	Doxorubicin	53
Conatumumab	DR5	Poly (lactic-co-glycolic acid) (PLGA)	-	22
Trastuzumab	HER2/neu	Polycaprolactone- polyethylene glycol (PCL-PEG)	AMO-21 /5-Fu	54
Cetuximab	EGFR	Liposomes	Celecoxib	48
Cetuximab	EGFR	Micelles	IR-780 iodide	55
Cetuximab	EGFR	Carbon nanotubes	7-Ethyl-10-hydroxy-camptothecin	49
Adecatumumab	EpCAM	-	-	11
Dalotuzumab	IGF-1R	-	-	56
Drozitumab	DR5	-	-	57
Edrecolomab	EpCAM	-	-	58
Ensituximab	MUC5AC	-	-	59
Etaracizumab	αVβ3 integrin	-	-	11
Necitumumab	EGFR	-	-	60

limitations of cancer chemotherapy can be overcome through the utilization of nanotechnology-based therapeutics. For this objective, developing actively targeted nanotherapy against overexpressed molecular markers on the CRC cells utilizing the nanoformulation of therapeutic mAbs by nanocarriers can represent great potentiality. The employment of nanomaterials can improve the pharmacokinetic properties of anticancer agents and provide effective and selective treatment for multidrug-resistant cancers.

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Ethical statement
There is none to be declared.

Competing interests
The authors declare no competing interests.

Authors' contribution
MHS conceived the original idea and supervised the project. AS and MAK contributed to the conceptualization of the manuscript and to the overall writing and editing of the manuscript. MAK collected the data and drafted the manuscript. All authors discussed the contents and contributed to the final manuscript.

References

1. Zarour LR, Anand S, Billingsley KG, Bisson WH, Cercek A, Clarke MF, *et al.* Colorectal Cancer Liver Metastasis: Evolving Paradigms and Future Directions. *Cell Mol Gastroenterol Hepatol* **2017**; 3: 163-73. doi:10.1016/j.jcmgh.2017.01.006
2. Mirinezhad SK, Moaddab SY, Shirazi KM, Bonyadi MJ, Eftekharsadat AT, Grami SMN, et al. Clinical and Genetic Characterization of Familial Adenomatous Polyposis: An Iranian Population Study. *Iranian Red Crescent Medical Journal* **2018**; 20(4);e64254. doi:10.5812/ircmj.64254
3. Mirinezhad SK, Mousavi F, Baghri M, Sepehri B, Ghavidel A, Ghojazadeh M, et al. Congenital Hypertrophy of Retinal Pigment Epithelium for Diagnosis of Familial Adenomatous Polyposis - the First FAP registry in Iran. *Asian Pac J Cancer Prev* **2018**; 19: 167-9. doi:10.22034/apjcp.2018.19.1.167
4. Mishra J, Drummond J, Quazi SH, Karanki SS, Shaw JJ, Chen B, et al. Prospective of colon cancer treatments and scope for combinatorial approach to enhanced cancer cell apoptosis. *Crit Rev Oncol Hematol* **2013**; 86: 232-50. doi:10.1016/j.critrevonc.2012.09.014
5. Gillet JP, Gottesman MM. Mechanisms of multidrug resistance in cancer. *Methods Mol Biol* **2010**; 596: 47-76. doi:10.1007/978-1-60761-416-6_4
6. Bregoli L, Movia D, Gavigan-Imedio JD, Lysaght J, Reynolds J, Prina-Mello A. Nanomedicine applied to translational oncology: A future perspective on cancer treatment. *Nanomedicine* **2016**; 12: 81-103. doi:10.1016/j.nano.2015.08.006
7. Omidi Y, Barar J. Impacts of blood-brain barrier in drug delivery and targeting of brain tumors. *Bioimpacts* **2012**; 2: 5-22. doi:10.5681/bi.2012.002
8. Barar J, Omidi Y. Dysregulated pH in Tumor Microenvironment Checkmates Cancer Therapy. *Bioimpacts* **2013**; 3: 149-62. doi:10.5681/bi.2013.036
9. Omidi Y, Barar J. Targeting tumor microenvironment: crossing tumor interstitial fluid by multifunctional nanomedicines. *Bioimpacts* **2014**; 4: 55-67. doi:10.5681/bi.2014.021
10. Yu B, Tai HC, Xue W, Lee LJ, Lee RJ. Receptor-targeted nanocarriers for therapeutic delivery to cancer. *Mol Membr Biol* **2010**; 27: 286-98. doi:10.3109/09687688.2010.521200
11. Noguchi T, Ritter G, Nishikawa H. Antibody-based therapy in colorectal cancer. *Immunotherapy* **2013**; 5: 533-45. doi:10.2217/imt.13.35
12. Omidi Y, Barar J. Induction of human alveolar epithelial cell growth factor receptors by dendrimeric nanostructures. *Int J Toxicol* **2009**; 28: 113-22. doi:10.1177/1091581809335177
13. Spano JP, Fagard R, Soria JC, Rixe O, Khayat D, Milano G. Epidermal growth factor receptor signaling in colorectal cancer: preclinical data and therapeutic perspectives. *Ann Oncol* **2005**; 16: 189-94. doi:10.1093/annonc/mdi057
14. Baradaran B, Majidi J, Farajnia S, Barar J, Omidi Y. Targeted therapy of solid tumors by monoclonal antibody specific to epidermal growth factor receptor. *Hum Antibodies* **2014**; 23: 13-20. doi:10.3233/hab-140278
15. Winder T, Lenz HJ. Vascular endothelial growth factor and epidermal growth factor signaling pathways as therapeutic targets for colorectal cancer. *Gastroenterology* **2010**; 138: 2163-76. doi:10.1053/j.gastro.2010.02.005
16. Yarom N, Jonker DJ. The role of the epidermal growth factor receptor in the mechanism and treatment of colorectal cancer. *Discov Med* **2011**; 11: 95-105.
17. Bendardaf R, El-Serafi A, Syrjanen K, Collan Y, Pyrhonen S. The effect of vascular endothelial growth factor-1 expression on survival of advanced colorectal cancer patients. *Libyan J Med* **2017**; 12: 1290741. doi:10.1080/19932820.2017.1290741
18. Tabernero J. The role of VEGF and EGFR inhibition: implications for combining anti-VEGF and anti-EGFR agents. *Mol Cancer Res* **2007**; 5: 203-20. doi:10.1158/1541-7786.mcr-06-0404
19. Majidi J, Barar J, Baradaran B, Abdolalizadeh J, Omidi Y. Target therapy of cancer: implementation of monoclonal antibodies and nanobodies. *Hum Antibodies* **2009**; 18: 81-100. doi:10.3233/hab-2009-0204
20. Zhang X, Li Y, Li H, Qin Y, Bai C, Xu F, et al. Combined EGFR and VEGFR versus single EGFR signaling pathways inhibition therapy for NSCLC: a systematic review and meta-analysis. *PLoS One* **2012**; 7: e40178. doi:10.1371/journal.pone.0040178
21. McLornan DP, Barrett HL, Cummins R, McDermott U, McDowell C, Conlon SJ, et al. Prognostic significance of TRAIL signaling molecules in stage II and III colorectal cancer. *Clin Cancer Res* **2010**; 16: 3442-51. doi:10.1158/1078-0432.ccr-10-0052
22. Fay F, McLaughlin KM, Small DM, Fennell DA, Johnston PG, Longley DB, et al. Conatumumab (AMG 655) coated nanoparticles for targeted pro-apoptotic drug delivery. *Biomaterials* **2011**; 32: 8645-53. doi:10.1016/j.biomaterials.2011.07.065
23. Bavi P, Prabhakaran SE, Abubaker J, Qadri Z, George T, Al-Sanea N, et al. Prognostic significance of TRAIL death receptors in Middle Eastern colorectal carcinomas and their correlation to oncogenic KRAS alterations. *Mol Cancer* **2010**; 9: 203. doi:10.1186/1476-4598-9-203
24. Duiker EW, van der Zee AG, de Graeff P, Boersma-van Ek W, Hollema H, de Bock GH, et al. The extrinsic apoptosis pathway and its prognostic impact in ovarian cancer. *Gynecol Oncol* **2010**; 116: 549-55. doi:10.1016/j.ygyno.2009.09.014
25. Rosa B, de Jesus JP, de Mello EL, Cesar D, Correia MM. Effectiveness and safety of monoclonal antibodies for metastatic colorectal cancer treatment: systematic review and meta-analysis. *Ecancermedicalscience* **2015**; 9: 582. doi:10.3332/ecancer.2015.582
26. Cohen SJ, Cohen RB, Meropol NJ. Targeting signal transduction pathways in colorectal cancer--more than skin deep. *J Clin Oncol* **2005**; 23: 5374-85. doi:10.1200/jco.2005.02.194
27. Esfahani A, Somi MH, Ayromlou H, Nikanfar A, Jafarabadi MA, Sadat BE, et al. The effect of n-3 polyunsaturated fatty acids on incidence and severity of oxaliplatin induced peripheral neuropathy: a randomized controlled trial. *Biomark Res* **2016**; 4: 13. doi:10.1186/s40364-016-0066-3
28. van Helden EJ, Menke-van der Houven van Oordt CW, Heymans MW, Ket JCF, van den Oord R, Verheul HMW. Optimal use of anti-EGFR monoclonal antibodies for patients with advanced colorectal cancer: a meta-analysis. *Cancer Metastasis Rev* **2017**; 36: 395-406. doi:10.1007/s10555-017-9668-y
29. Redman JM, Hill EM, AlDeghaither D, Weiner LM. Mechanisms of action of therapeutic antibodies for cancer. *Mol Immunol* **2015**; 67: 28-45. doi:10.1016/j.molimm.2015.04.002
30. Sanchez-Martin D, Sorensen MD, Lykkemark S, Sanz L, Kristensen P, Ruoslahti E, et al. Selection strategies for anticancer antibody discovery: searching off the beaten path. *Trends Biotechnol* **2015**; 33: 292-301. doi:10.1016/j.tibtech.2015.02.008
31. Ocana A, Pandiella A. Targeting HER receptors in cancer. *Curr Pharm Des* **2013**; 19: 808-17.
32. Montagut C, Argiles G, Ciardiello F, Poulsen TT, Dienstmann R, Kragh M, et al. Efficacy of Sym004 in Patients With Metastatic Colorectal Cancer With Acquired Resistance to Anti-EGFR Therapy and Molecularly Selected by Circulating Tumor DNA Analyses: A Phase 2 Randomized Clinical Trial. *JAMA Oncol* **2018**; 4: e175245. doi:10.1001/jamaoncol.2017.5245
33. Khiavi MA, Safary A, Aghanejad A, Barar J, Rasta SH, Golchin A, et al. Enzyme-conjugated gold nanoparticles for combined enzyme and photothermal therapy of colon cancer cells. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* **2019**; 572: 333-44. doi:10.1016/j.colsurfa.2019.04.019
34. Zhao B, Wang L, Qiu H, Zhang M, Sun L, Peng P, et al. Mechanisms of resistance to anti-EGFR therapy in colorectal cancer. *Oncotarget* **2017**; 8: 3980-4000. doi:10.18632/oncotarget.14012
35. De Angelis ML, Bruselles A, Francescangeli F, Pucilli F, Vitale S, Zeuner A, et al. Colorectal cancer spheroid biobanks: multi-level approaches to drug sensitivity studies. *Cell Biol Toxicol* **2018**. doi:10.1007/s10565-018-9423-3
36. Rodriguez-Ruiz V, Salatti-Dorado JA, Barzegari A, Nicolas-Boluda A, Houaoui A, Caballo C, et al. Astaxanthin-Loaded Nanostructured Lipid Carriers for Preservation of Antioxidant

Activity. *Molecules* **2018**; 23. doi:10.3390/molecules23102601
37. Patel NR, Pattni BS, Abouzeid AH, Torchilin VP. Nanopreparations to overcome multidrug resistance in cancer. *Adv Drug Deliv Rev* **2013**; 65: 1748-62. doi:10.1016/j.addr.2013.08.004
38. Matthaiou EI, Barar J, Sandaltzopoulos R, Li C, Coukos G, Omidi Y. Shikonin-loaded antibody-armed nanoparticles for targeted therapy of ovarian cancer. *Int J Nanomedicine* **2014**; 9: 1855-70. doi:10.2147/ijn.s51880
39. Babu A, Templeton AK, Munshi A, Ramesh R. Nanodrug delivery systems: a promising technology for detection, diagnosis, and treatment of cancer. *AAPS PharmSciTech* **2014**; 15: 709-21. doi:10.1208/s12249-014-0089-8
40. Safary A, Akbarzadeh Khiavi M, Omidi Y, Rafi MA. Targeted enzyme delivery systems in lysosomal disorders: an innovative form of therapy for mucopolysaccharidosis. *Cell Mol Life Sci* **2019**. doi:10.1007/s00018-019-03135-z
41. Safary A, Moniri R, Hamzeh-Mivehroud M, Dastmalchi S. Identification and Molecular Characterization of Genes Coding Pharmaceutically Important Enzymes from Halo-Thermo Tolerant Bacillus. *Adv Pharm Bull* **2016**; 6: 551-61. doi:10.15171/apb.2016.069
42. Safary A, Moniri R, Hamzeh-Mivehroud M, Dastmalchi S. Highly efficient novel recombinant L-asparaginase with no glutaminase activity from a new halo-thermotolerant Bacillus strain. *Bioimpacts* **2019**; 9: 15-23. doi:10.15171/bi.2019.03
43. Misra R, Acharya S, Sahoo SK. Cancer nanotechnology: application of nanotechnology in cancer therapy. *Drug Discov Today* **2010**; 15: 842-50. doi:10.1016/j.drudis.2010.08.006
44. Safary A, Akbarzadeh Khiavi M, Mousavi R, Barar J, Rafi MA. Enzyme replacement therapies: what is the best option? *Bioimpacts* **2018**; 8: 153-7. doi:10.15171/bi.2018.17
45. Bruno JG. Predicting the Uncertain Future of Aptamer-Based Diagnostics and Therapeutics. *Molecules* **2015**; 20: 6866-87. doi:10.3390/molecules20046866
46. Pietersz GA, Wang X, Yap ML, Lim B, Peter K. Therapeutic targeting in nanomedicine: the future lies in recombinant antibodies. *Nanomedicine (Lond)* **2017**; 12: 1873-89. doi:10.2217/nnm-2017-0043
47. Leung SL, Zha Z, Cohn C, Dai Z, Wu X. Anti-EGFR antibody conjugated organic-inorganic hybrid lipid nanovesicles selectively target tumor cells. *Colloids Surf B Biointerfaces* **2014**; 121: 141-9. doi:10.1016/j.colsurfb.2014.06.011
48. Limasale YD, Tezcaner A, Ozen C, Keskin D, Banerjee S. Epidermal growth factor receptor-targeted immunoliposomes for delivery of celecoxib to cancer cells. *Int J Pharm* **2015**; 479: 364-73. doi:10.1016/j.ijpharm.2015.01.016
49. Lee PC, Chiou YC, Wong JM, Peng CL, Shieh MJ. Targeting colorectal cancer cells with single-walled carbon nanotubes conjugated to anticancer agent SN-38 and EGFR antibody. *Biomaterials* **2013**; 34: 8756-65. doi:10.1016/j.biomaterials.2013.07.067
50. Li Y, Duo Y, Zhai P, He L, Zhong K, Zhang Y, et al. Dual targeting delivery of miR-328 by functionalized mesoporous silica nanoparticles for colorectal cancer therapy. *Nanomedicine (Lond)* **2018**. doi:10.2217/nnm-2017-0353
51. Cho YS, Yoon TJ, Jang ES, Soo Hong K, Young Lee S, Ran Kim O, et al. Cetuximab-conjugated magneto-fluorescent silica nanoparticles for in vivo colon cancer targeting and imaging. *Cancer Lett* **2010**; 299: 63-71. doi:10.1016/j.canlet.2010.08.004
52. Lin CY, Yang SJ, Peng CL, Shieh MJ. Panitumumab-Conjugated and Platinum-Cored pH-Sensitive Apoferritin Nanocages for Colorectal Cancer-Targeted Therapy. *ACS Appl Mater Interfaces* **2018**; 10: 6096-106. doi:10.1021/acsami.7b13431
53. Mamot C, Ritschard R, Kung W, Park JW, Herrmann R, Rochlitz CF. EGFR-targeted immunoliposomes derived from the monoclonal antibody EMD72000 mediate specific and efficient drug delivery to a variety of colorectal cancer cells. *J Drug Target* **2006**; 14: 215-23. doi:10.1080/10611860600691049
54. Hu N, Yin JF, Ji Z, Hong Y, Wu P, Bian B, et al. Strengthening Gastric Cancer Therapy by Trastuzumab-Conjugated Nanoparticles with Simultaneous Encapsulation of Anti-MiR-21 and 5-Fluorouridine. *Cell Physiol Biochem* **2017**; 44: 2158-73. doi:10.1159/000485955
55. Shih YH, Luo TY, Chiang PF, Yao CJ, Lin WJ, Peng CL, et al. EGFR-targeted micelles containing near-infrared dye for enhanced photothermal therapy in colorectal cancer. *J Control Release* **2017**; 258: 196-207. doi:10.1016/j.jconrel.2017.04.031
56. Sclafani F, Kim TY, Cunningham D, Kim TW, Tabernero J, Schmoll HJ, et al. A Randomized Phase II/III Study of Dalotuzumab in Combination With Cetuximab and Irinotecan in Chemorefractory, KRAS Wild-Type, Metastatic Colorectal Cancer. *J Natl Cancer Inst* **2015**; 107: djv258. doi:10.1093/jnci/djv258
57. Rocha Lima CM, Bayraktar S, Flores AM, MacIntyre J, Montero A, Baranda JC, et al. Phase Ib study of drozitumab combined with first-line mFOLFOX6 plus bevacizumab in patients with metastatic colorectal cancer. *Cancer Invest* **2012**; 30: 727-31. doi:10.3109/07357907.2012.732163
58. Schmoll HJ, Arnold D. When wishful thinking leads to a misty-eyed appraisal: the story of the adjuvant colon cancer trials with edrecolomab. *J Clin Oncol* **2009**; 27: 1926-9. doi:10.1200/jco.2008.20.6284
59. Beg MS, Azad NS, Patel SP, Torrealba J, Mavroukakis S, Beatson MA, et al. A phase 1 dose-escalation study of NEO-102 in patients with refractory colon and pancreatic cancer. *Cancer Chemother Pharmacol* **2016**; 78: 577-84. doi:10.1007/s00280-016-3108-5
60. Kuenen B, Witteveen PO, Ruijter R, Giaccone G, Dontabhaktuni A, Fox F, et al. A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies. *Clin Cancer Res* **2010**; 16: 1915-23. doi:10.1158/1078-0432.ccr-09-2425