Non-coding RNAs and resistance to anticancer drugs in gastrointestinal tumours

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NV and JH idea, conception and writing parts of the review.

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Abstract

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In this review we summarise the role of non-coding RNAs for different mechanisms resulting in drug resistance (e.g. drug transport, drug metabolism, cell cycle regulation, regulation of apoptotic pathways, cancer stem cells and epithelial-mesenchymal transition) in the context of gastrointestinal cancers.

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Abstract:

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Introduction:

Gastrointestinal (GI) cancer encompasses a heterogeneous group of tumours that affect the digestive tract system (Pourhoseingholi et al., 2015). These include cancers of the oesophagus, stomach, gallbladder, liver and biliary tract, pancreas, small intestine, colon, rectum and anus. GI cancer is the most common form of cancer responsible for nearly 25% of all new cancer diagnosis and responsible for most of cancer related death (around 30% of all cancer related death) worldwide (Siegel et al., 2015;Torre et al., 2015).

Chemotherapy is, alongside with surgery and radiation therapy, one of the main treatments for cancer (Hung et al., 2006;Chan et al., 2016;Ismael et al., 2016;Jakhetiya et al., 2016;Murphy, 2016;Olcina and Giaccia, 2016;Rautio et al., 2016;Ristamaki and Algars, 2016;Rutkowski and Hompes, 2016). Many chemotherapeutic agents have successfully prolonged overall and progression-free survival of GI cancer patients (Slamon et al., 2001;Motzer et al., 2007;Blanke et al., 2008;Maemondo et al., 2010;Chapman et al., 2011). In addition, a better understanding of the biology and mechanism underpinning GI cancer initiation and progression is leading to more personalised treatments. Indeed, identification of

well-defined molecular subtypes and/or molecular profiling of somatic mutations offer the opportunity to further optimize the efficacy of treatments through tailored approaches (Kwak et al., 2010;Douillard et al., 2013;Korpanty et al., 2014;Siroy et al., 2015).

Despite major improvements in the management of GI cancer patients, resistance to therapies arises almost inevitably at some point during the treatment and chemo-resistance is one of the main challenges in cancer therapy (Housman et al., 2014). Drug resistance can be caused by gene mutations, abnormal DNA repair, alteration in cell cycle regulation, cell death inhibition (mostly caused by deregulated apoptotic signalling pathways), reduced drug efficacy as well as enhanced drug clearance (Zahreddine and Borden, 2013;Housman et al., 2014). Furthermore, the epithelial-mesenchymal transition (EMT) process and the presence of tumour stem cells have been identified as causes of drug resistance (Shang et al., 2013;Xia and Hui, 2014;Mitra et al., 2015;Prieto-Vila et al., 2017). The complex molecular mechanisms of chemo-resistance have not been fully elucidated yet and a better understanding of drivers of primary and secondary resistance to chemotherapy will likely result into improved patients' survival. Increasing evidence points towards the role of non-coding RNAs as a central hub for treatment resistance. Therefore, this review outlines the role of non-coding RNAs for the different drug resistance mechanisms involved in GI cancer therapy failure. Table 1 summarised the non-coding RNAs discussed in this review and in figure 1-6 the role for each of these non-coding RNAs in the context of the different GI tumours is illustrated.

Non-coding RNAs:

In human tissues the amount of non-coding RNAs is more than three times higher compared to the amount of protein-coding RNAs (Geisler and Coller, 2013). Non-coding RNAs are a large family that includes more than 16 categories of long and short RNA molecules (Table 2); among them transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small nucleolar RNAs (snoRNAs), endogenous small interfering RNAs (endo-siRNAs), sno-derived RNAs (sdRNAs), transcription initiation RNAs (tiRNAs), miRNA-offset-RNAs (moRNAs), circular RNAs (circRNAs), vault RNAs (vRNAs), microRNAs, small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), extracellular RNAs (exRNAs), piwi-interacting RNAs (piRNAs), small Cajal body RNAs (scaRNAs), long intergenic non-coding RNAs

(lincRNAs) and long non-coding RNAs (lncRNAs), all of which are not coding for known proteins (Taal et al., 1993;Eddy, 2001;He and Hannon, 2004;Guttman et al., 2009;Langenberger et al., 2009;Taft et al., 2009a;Taft et al., 2009b;Wilusz et al., 2009;Choudhuri, 2010;Ling et al., 2013;Claycomb, 2014;Guo et al., 2014;An et al., 2016;Azlan et al., 2016;Beermann et al., 2016;de Almeida et al., 2016;Evans et al., 2016;Geiger and Dalgaard, 2016;Granados-Riveron and Aquino-Jarquin, 2016;Khurana et al., 2016;Qi et al., 2016;Quinn and Chang, 2016).

Long non-coding RNAs (lncRNAs) and microRNAs are the most studied non-coding RNAs playing a role in anticancer drug resistance and will be covered in this review.

LncRNAs are composed of more than 200 nucleotides. They are important regulators during development and pathological processes (Guttman et al., 2011;Sauvageau et al., 2013;Herriges et al., 2014;Li et al., 2014a;Ounzain et al., 2014). LncRNAs are pivotal in regulating gene expression by binding to chromatin regulatory proteins and they are able to alter chromatin modification as well as transcriptional or post-transcriptional gene regulation by interacting with other RNAs and proteins (Moran et al., 2012;Kornienko et al., 2013;Han and Chang, 2015). Recently, a crosstalk and strong linkage between lncRNA and microRNAs has been identified (Yoon et al., 2014). It has been shown that lncRNA stability can be reduced by interaction with specific microRNAs and, *vice versa,* lncRNAs act as microRNA decoys sequestering microRNAs from the intra-cellular cytosol and leading to re-expression of microRNA target genes (Yoon et al., 2014). Furthermore, lncRNAs can promote gene expression by competing with microRNAs for specific binding sites in the non-coding regions of mRNAs and prevent the transcriptional repression caused by microRNAs (Yoon et al., 2014). Interestingly some lncRNAs can be processed into microRNAs (Yoon et al., 2014) suggesting a plastic interaction among different classes of non-coding RNAs.

MicroRNAs are short RNA transcripts of 18–24 nucleotides. They are responsible for fine tuning cell homeostasis by controlling gene expression at post-transcriptional level, (Fabbri et al., 2009;Valeri et al., 2009;Winter et al., 2009). Due to the fact that each microRNAs can have several target mRNAs the interaction of one microRNA with various target mRNAs results in direct deregulation of different target proteins acting simultaneously in regulation of diverse cellular pathways (Macfarlane and Murphy, 2010;Pasquinelli, 2012). Therefore, variation in microRNA expression can result in reduced mRNA levels ultimately resulting in

changes in protein levels within the cell (von Schack et al., 2011;Pasquinelli, 2012). MicroRNAs expression patterns are tissue-specific (Lagos-Quintana et al., 2002) and often define the physiological status of the cell (Lim et al., 2005). Strong clinical and pre-clincial evidence suggests that microRNA aberrant expression plays a role in several diseases including cancer, infectious, neurodegenerative and immune-related diseases. (Murakami et al., 2006;Mitchell et al., 2008;O'Connell et al., 2010;Esteller, 2011;Ha, 2011b;a;c;Grasedieck et al., 2012;Iorio and Croce, 2012;Acunzo et al., 2015;Balatti et al., 2015;Gardiner et al., 2015). Analysis of microRNA expression patterns represents a promising tool for cancer diagnosis, prognosis and treatment prediction. MicroRNAs have been extensively studied in monitoring treatment resistance in consideration of their high stability in tissues and body fluids. In blood, microRNAs are included in RNA-binding multiprotein complexes and/or exosomes and their short length makes microRNAs less prone to degradation and improves their stability under different sample storage conditions in blood (Mitchell et al., 2008;Macfarlane and Murphy, 2010;Grasedieck et al., 2012;Gardiner et al., 2015) .

General principles of drug resistance:

Drug resistance is classified into intrinsic and acquired. Primary drug resistance is pre-existing and renders cancer cells immune against the therapy from the very beginning. In contrast, acquired (secondary) drug resistance develops during therapy due to adaptive processes of the tumour (Gottesman et al., 2002;Longley and Johnston, 2005;Rodrigues et al., 2012a;Holohan et al., 2013;Housman et al., 2014). Different mechanisms are involved in primary and acquired drug resistance and relate to non-coding RNAs dysregulation.

Deregulation of proteins involved in drug metabolism

One reason for drug resistance can be found on the level of drug transport. Reduced influx or increased efflux of chemotherapeutics result in lower intracellular drug concentrations and promotes therapy failure (Gottesman et al., 2002). Altered drug metabolism is another possible cause for drug resistance. Drug metabolism is a complex pathway composed of

multiple proteins for detoxification of foreign compounds (*e.g.* chemotherapeutics) normally neither produced nor present in a cell (Michael and Doherty, 2005). This pathway can be subdivided into modification (phase I reaction), conjugation (phase II reaction) and excretion (phase III reaction) (Park, 2001). Several drug-metabolizing enzymes, especially members of the cytochrome P450 family, together with drug transporters increase the polarity of the drugs during phase I (Shimada et al., 1989;Guengerich and Shimada, 1991) . In the following phase II the polarity of the drugs is further increased by conjugation reactions (Shea et al., 1988b;McLellan and Wolf, 1999b). Finally, in phase III the resulting drug metabolites are exported by transmembrane transporter like ATP-binding cassette (ABC) proteins and solute carrier (SLC) transport proteins (Dean et al., 2001;Kathawala et al., 2015;Lin et al., 2015;Colas et al., 2016).

The vaults are known to contribute to drug resistance by transporting drugs away from their intracellular targets and vaults are involved in drug sequestration (Mossink et al., 2003). The vRNAs hvg-1 and hvg-2 that are present in the vaults (Table 2) interact with drugs via specific binding sites (Gopinath et al., 2010). In agreement with their role in regard to drug resistance the number of vaults are increased in cancer patients who developed resistance under chemotherapy (Mossink et al., 2003). In addition, the vRNAs are producing several small RNAs among them is svRNAb which down-regulates the key enzyme in drug metabolism CYP3A4 and accounts so for multidrug resistance in GI cancers (Persson et al., 2009).

Furthermore, lncRNA H19 was identified as another non-coding RNA involved in drug resistance. The oncogenic potential of lncRNA H19 was demonstrated in different tumour types (*e.g.* liver and oesophageal cancer) and over-expression of lncRNA H19 was observed in parallel with up-regulation of the membrane glycoprotein p95 in multidrug-resistant tumours (Tsang and Kwok, 2007;Matouk et al., 2013). In liver tumour cells resistant to doxorubicin, etoposide, paclitaxel and vincristine lncRNA H19 expression was increased (Tsang and Kwok, 2007). LncRNA H19 participate in the regulation of *MDR1* gene (also known as *ABCB1* gene) expression and modulate the drug transport out of the cell (Tsang and Kwok, 2007). *In-vitro* models of hepatocellular carcinoma suggest that lncRNA H19 can alter

MDR1 promoter methylation and, in doing so, increases the transcription of P-glycoprotein (Tsang and Kwok, 2007).

Similarly, in gastric cancer, lncRNA MRUL (MDR-related and up-regulated lncRNA) acts as an enhancer for transcription of P-glycoprotein (MDR1) (Wang et al., 2014) increasing the number of transmembrane transporters on the tumour cell membrane and fosters the drug export (Wang et al., 2014). As we described above, different non-coding RNAs can merge onto the same pathway: this is the case of lncRNA AK022798 whose expression is induced by NOTCH-1 over-expression during gastric cancer progression (Hang et al., 2015). LncRNA AK022798 in turn up-regulates the expression of P-glycoprotein and is responsible for increased cisplatin resistance in gastric cancer patients (Hang et al., 2015). Similarly, in cisplatin and 5-fluorouracil resistant gastric cancer patients the expression of lncRNA PVT-1 (plasmacytoma variant translocation 1) and lncRNA ANRIL (antisense to CDKN2B locus) are also increased and these non-coding RNAs promote MDR1 up-regulation and drug resistance (Zhang et al., 2015b;Lan et al., 2016).

Non-coding RNA dysregulation is tissue specific, indeed Wnt-β-catenin pathway activation triggers the expression of a different lncRNA, CCAL (colorectal cancer-associated lncRNA. The effect on phenotype is the same as in other cancers given CCAL in turn up-regulates P-glycoprotein expression and causing chemotherapy resistance (Ma et al., 2016b).

Additional to the regulation via lncRNAs ABC transporter expression levels are also controlled by miRNAs (Haenisch et al., 2014;Ikemura et al., 2014).

In colon cancer, P-glycoprotein expression was found to be directly deregulated at post-transcriptional level by binding of miR-145 to the 3`-UTR of the *MDR1* gene transcript (Ikemura et al., 2013). Down-regulation of miR-145 results in increased ABCB1 protein level (Ikemura et al., 2013). Analogously miR-297 binds to the 3´-UTR of ABCC2 mRNA and supresses the expression of ABCC2 transporter (Xu et al., 2012). In chemo-resistant colorectal carcinoma, miR-297 is often down-regulated and consequently ABCC2 is expressed on a higher level compared to the surrounding colon tissue (Xu et al., 2012). Interestingly, *in-vitro* and *in-vivo* models suggest that resistance to vincristine and oxaliplatin could be overcome by restoring miR-297 expression in therapy resistant cells (Xu et al., 2012). Virtually expression of all the transporters can be affected by microRNA dysregulation; ABCB5 transporter is highly expressed in colon cancer cell lines with down-

regulated miR-522 expression and renders these cells resistant to doxorubicin treatment (Yang et al., 2015). MiR-522 binds to the ABCB5 mRNA 3´-UTR and over-expression of miR-522 reverse chemo-resistance to doxorubicin (Yang et al., 2015). Similarly, 5-fluorouracil resistance in microsatellite instable colon cancer (caused by deregulated miR-21 or miR-155 (Valeri et al., 2010a;Valeri et al., 2010b) as mentioned in detail later) can be enhanced by down-regulation of miR-23a resulting in higher expression of the direct target ABCF1 (Li et al., 2015d).

Similar examples exist across the board: in gastric cancer for example, down-regulation of miR-508-5p was identified as a reason for multidrug resistance (Shang et al., 2014). MiR-508-5p represses the expression of P-glycoprotein and the transcription factor zinc ribbon domain-containing 1 (ZNRD1) that is an important factor for *MDR1* gene translation (Shang et al., 2014). Loss of miR-508-5p decreased drug sensitivity in gastric cancer *in-vitro* and *in-vivo,* whereas ectopic expression of miR-508-5p overcomes drug resistance (Shang et al., 2014).

In pancreatic cancer cell lines, expression of the transporter ABCC1 is controlled by miR-1291 binding to the 3´-UTR (Pan et al., 2013). MiR-1291 is often down-regulated in pancreatic cancer resulting in an increased expression of ABCC1 that finally leads to higher efflux rate of toxic substances (Munoz et al., 2007;Tu et al., 2016). This is the reason for resistance to many chemotherapeutics, such as anthracyclines (*e.g.*, doxorubicin), platinum derivates and the folate antagonist methotrexate (Munoz et al., 2007;Tu et al., 2016). Another transporter, called ATP7A (ATPase Cu^{2+} transporting alpha polypeptide), is up-regulated in *in-vitro* models of resistant pancreatic tumours due to decreased expression of miR-374b (Schreiber et al., 2016) and increased ATP7A protein expression is at least partially responsible for cisplatin resistance in pancreatic cancer model systems (Schreiber et al., 2016).

Down-regulation of miR-122 in liver tumours results in high expression of ABC transporter proteins and causes increased drug export of doxorubicin in liver cancer patients (Xu et al., 2011). Similarly, ABCB1 transporter expression is up-regulated in hepatocellular cancer cells when the post-transcriptional regulator miR-223 is down-regulated and the result is again resistance to doxorubicin treatment (Yang et al., 2013b).

Down-regulation of microRNAs let-7g and let-7i results in increased expression of ABCC10 that in turn is responsible for resistance to cisplatin therapy in oesophageal cancer patients (Wu et al., 2016a).

An important barrier for oral anticancer drugs is represented by intestinal epithelial cells of the GI tract (Ikemura et al., 2014;Peterson and Artis, 2014). The absorption of most nutrient components as well as drugs is related to a variety of influx transporters such as members of the SLC transporter family (Ikemura et al., 2014). The expression pattern of the SLC transporter varied according to the differentiation status of intestinal epithelial cells which is controlled by microRNAs (McKenna et al., 2010). Therefore, changes in the expression level of microRNAs have most probably an important influence on the drug up-take rate (McKenna et al., 2010). Up to now the role of microRNAs for the expression level of SLC transporter have been studied only in cell culture models for colon carcinoma, liver, pancreatic and gastric tumours (Dalmasso et al., 2011;Pullen et al., 2011). In colon cancer cells expression of miR-92b reduce the amount of SLC15A and SLC15A1 transporter resulting in decreased drug absorption (Dalmasso et al., 2011). In the context of liver and pancreatic tumours miR-29a, miR-29b and miR-124 target SLC16A1 and reduce the expression of this transporter (Pullen et al., 2011). Recently it was shown that miR-939 targets direct SLC34A2 in gastric cancer (Zhang et al., 2017). In 5-fluorouracil resistant gastric cancer miR-939 is down-regulated and results in increased expression level of SLC34A2. The transport protein SLC34A2 acts as mediator of miR-939 and activates the Ras/MEK/ERK pathway which is known to be deregulated often in cancer and to cause resistance to chemotherapy (Zhang et al., 2017). In *in-vitro* models of gastric cancer over-expression of miR-939 strongly decreased MEK1/2 phosphorylation as well as Raf-1 level, whereas SLC34A2 restoration rescued these effects (Zhang et al., 2017).

Also for some drug-metabolizing enzymes post-transcriptional regulations by miRNAs have been proven (Tsuchiya et al., 2006;Koturbash et al., 2012;Ikemura et al., 2014). Due to their pivotal role in maintaining chemical and functional homeostasis of cells, cytochrome P450 enzymes are strictly controlled. Under physiological conditions, cytochrome P450 enzymes are involved in the regulation of endogenous molecules like bile acids and steroids and under pathological conditions in the case of chemotherapy these enzymes are important in regard to

drug metabolism. De-regulated expression of cytochrome P450 enzymes is linked to drug resistance and therapy failure (Rendic and Guengerich, 2015).

For example, miR-378 targets mRNA coding for CYP2E1 and reduces the expression level of CYP2E1 protein in cell culture models of liver tumours (Mohri et al., 2010;Zhou et al., 2016). In liver cancer patients CYP2E1 expression is increased while miR-378 is down-regulated (Mohri et al., 2010;Zhou et al., 2016). Also, a direct regulation of CYP1B1 by miR-27b was demonstrated in hepatocellular cancer cell lines (An et al., 2017). Decreased expression of miR-27b results in high expression level of CYP1B1 and renders by this liver tumour resistant to docetaxel treatment (An et al., 2017).

In pancreatic cancer cells over-expression of miR-27b leads to down-regulation of CYP3A4 protein and results in drug resistance to cyclophosphamide because CYP3A4 is necessary for drug activation (Pan et al., 2009). MicroRNA-based regulation of enzymes involved in phase II reactions are less analysed but nevertheless, in the context of oesophageal cancer, regulation of glutathione S-transferase P1 (GSTP1) was found to be regulated by miR-133a (Kano et al., 2010). Reduced expression of the tumour suppressor miR-133a resulted in increased level of GSTP1 protein (Kano et al., 2010). In phase II detoxification reactions - including inactivation of platinum derivates and alkylating reagents -GSTP1 catalyses the addition of glutathione to the drug activated during phase I reactions with electrophiles (Shea et al., 1988a;McLellan and Wolf, 1999a).

A more specific influence of non-coding RNAs on drug metabolism was demonstrated for 5-fluorouracil in liver and colon tumours (Offer et al., 2014;Chai et al., 2015). Dihydropyrimidine dehydrogenase, an important enzyme in 5-fluorouracil metabolism, is repressed by miR-494 in colon tumours and by miR-27a as well as miR-27b in liver cancer (Offer et al., 2014;Chai et al., 2015). The fact that the translation of one and the same enzyme in two different tissues is under the control of different miRNAs underlines the tissue-specific regulation and fine-tuning of protein expression that is exerted by miRNAs.

In liver cancer the translation of two of the most important targets of chemotherapeutic agents, dihydrofolate reductase and thymidylate synthase, are repressed by up-regulation of miR-215 (Wang et al., 2015b). Reduced expression of dihydrofolate reductase and thymidylate synthase leads to the development of insensitivity to doxorubicin treatment (Wang et al., 2015b).

Thymidylate synthase is the target of 5-fluoruracil therapy and this enzyme is down-regulated by increased expression of miR-192 and miR-215 in colon cancer patients (Boni et al., 2010). In this case altered microRNA expression results in down-modulation of the drug target and leads to therapy failure. In addition, miR-192 and miR-215 alter the cell-cycle control at multiple levels and prevent progression into the S-phase leading to 5-fluorouracil resistance (Boni et al., 2010).

A similar case was observed in pancreatic tumours where RRM2 (ribonucleotide reductase regulatory subunit M2) the target of gemcitabine is under direct control of miR-211 and let-7a (Bhutia et al., 2013;Maftouh et al., 2014). Decreased expression of miR-211 and let-7a results in higher RRM2 protein level and renders the tumours resistant to gemcitabine (Bhutia et al., 2013;Maftouh et al., 2014).

Deregulation of cell-cycle, DNA repair pathways and alteration in death pathways

Impaired cell cycle regulation and alteration of cell death pathways are common causes of drug resistance (Helleday et al., 2008;Rodrigues et al., 2012b). Increased cell cycle progression and reduced cell death rate lead to accumulation of mutations and uncontrolled cell proliferation, a hallmark of tumour cells (Hanahan and Weinberg, 2011). Errors in the DNA-damage response program pathways [nuclear excision repair (NER), base excision repair (BER), DNA mismatch repair (MMR)] play an important role in cancer progression and chemo-resistance (Hoeijmakers, 2001;Harper and Elledge, 2007;Jackson and Bartek, 2009;Pearl et al., 2015). A complex interaction interplay exists between non-coding RNAs and the DNA-damage pathways: on one hand the DNA-damage pathway induces the expression of several non-coding RNAs especially of microRNAs and on the other hand non-coding RNAs regulate directly the expression of several genes involved in DNA-damage pathway. This interaction is cell type specific and dependent on the intensity and nature of DNA damage (Pothof et al., 2009;Wouters et al., 2011;Chowdhury et al., 2013;Sharma and Misteli, 2013;Bottai et al., 2014).

LncRNA HOTAIR (HOX transcript antisense RNA) is highly expressed in a broad variety of solid tumours including liver, colorectal, pancreatic and gastrointestinal stromal tumours (Geng et al., 2011;Kogo et al., 2011;Niinuma et al., 2012). LncRNA HOTAIR reprogram

chromatin organization together with the polycomb repressive complex PRC2 (Kogo et al., 2011). Up-regulation of lncRNA HOTAIR results in higher expression level of members of the PRC2 complex (SUZ12, EZH2, and H3K27me3) (Kogo et al., 2011). Therefore, increased lncRNA HOTAIR expression is associated with a genome-wide reprogramming via PRC2 mediated epigenetic silencing of chromatin (Kogo et al., 2011). In addition lncRNA HOTAIR down-regulates cyclin-dependent kinase inhibitor 1 (p21(WAF/CIP1)) (Liu et al., 2013) causing the loss of an important regulator of the G_1 and S phase progression (el-Deiry et al., 1993;Waldman et al., 1995;Bunz et al., 1998). Due to the fact that p21(WAF/CIP1) represents a major target of p53 activity DNA damage in lncRNA HOTAIR expressing tumour cells don´t go into cell cycle arrest and this promote cisplatin resistance (el-Deiry et al., 1993;Waldman et al., 1995;Bunz et al., 1998;Liu et al., 2013).

In oesophageal, gastric, colorectal and hepatocellular cancer as well as cholangiocarcinomas, lncRNA TUG1 (taurine-up-regulated gene 1) is involved in causing resistance to chemotherapy (Huang et al., 2015;Dong et al., 2016;Jiang et al., 2016;Li et al., 2016b;Wang et al., 2016a;Zhang et al., 2016a;Xu et al., 2017c). In tumour tissue lncRNA TUG1 is up-regulated and promotes cell growth by increased transcription of the *Bcl-2* gene and epigenetic silencing of cyclin-dependent protein kinase inhibitors (p15, p16, p21, p27 and p57) and pro-apoptotic genes (caspase-3, caspase-9 and Bax) (Huang et al., 2015;Dong et al., 2016;Jiang et al., 2016;Li et al., 2016b;Wang et al., 2016a;Zhang et al., 2016a;Xu et al., 2017c). Therefore, lncRNA TUG1 is an excellent example for the fact that non-coding RNAs target simultaneously the expression of different genes; beside increasing the expression level of the anti-apoptotic protein Bcl-2, expression of key players in the caspase-mediated apoptosis pathway are inhibited together with different cyclin-dependent protein kinase inhibitors. This results in decreasing the G0/G1 arrest during cell cycle and reduces the apoptosis rate of the tumour cells. Most probably lncRNA TUG1 has also a role in the epithelial-mesenchymal transition (Wang et al., 2016a;Xu et al., 2017c) that increases resistance to drug treatments further as outlined in detail below.

Also, the lncRNA PANDAR (promoter of CDKN1A antisense DNA damage-activated RNA) is often deregulated in different GI tumours like gastric, colorectal and hepatocellular cancer as well as cholangiocarcinoma (Peng and Fan, 2015;Ma et al., 2016a;Lu et al., 2017a;Xu et al., 2017b). In all these tumours up-regulation of lncRNA PANDAR results in increased

proliferation rate and reduced apoptosis (Peng and Fan, 2015;Ma et al., 2016a;Lu et al., 2017a;Xu et al., 2017b). LncRNA PANDAR interacts with the transcription factor NF-YA, an important regulator for transcription of pro-apoptotic genes (Hung et al., 2011). This interaction between lncRNA PANDAR and NF-YA results in decreased expression of pro-apoptotic genes and eventually leads to drug resistance (Peng and Fan, 2015;Ma et al., 2016a;Lu et al., 2017a;Xu et al., 2017b).

LncRNA UCA1 (urothelial carcinoma associated1) mediates resistance to doxorubicin treatment in gastric cancer (Shang et al., 2016). In *in-vitro* systems knockdown of lncRNA UCA1 overcomes the doxorubicin resistance due to an increased expression of PARP and reduced expression of Bcl-2 resulting in higher apoptosis rate (Shang et al., 2016).

Furthermore, it was shown that lncRNA UCA1 sequesters miR-204-5p in colorectal cancer and reduces the level of this microRNA in cancer cells (Bian et al., 2016). The consequence is enhanced cell proliferation and 5-fluorouracil resistance (Bian et al., 2016).

Another example of non-coding RNAs influencing cell-cycle is lncRNA ARA (adriamycin resistance associated) (Jiang et al., 2014;Cox and Weinman, 2016). LncRNA ARA was found to be over-expressed in doxorubicin resistant liver cancer cell lines compared to the parental cell lines (Jiang et al., 2014). Down-regulation of lncRNA ARA results in cell-cycle arrest in G2/M phase, suppressed proliferation, increased apoptotic cell death and, as expected, a reduced resistance against doxorubicin (Jiang et al., 2014;Cox and Weinman, 2016). Furthermore, lncRNA ARA is involved in the regulation of multiple signalling pathways including the MAPK-pathway (Jiang et al., 2014;Cox and Weinman, 2016). Beside lncRNA ARA the lncRNA URHC (up-regulated in hepatocellular carcinoma) is found among the most up-regulated lncRNAs in hepatocellular carcinoma. One target of lncRNA URHC is the tumour-suppressor ZAK (Xu et al., 2014b). Down-regulation of ZAK via lncRNA URHC results in increased cell proliferation and inhibits apoptosis (Xu et al., 2014b).

In pancreatic cancer lncRNA HOTTIP (HOXA transcript at the distal tip) up-regulates the homeobox-transcription factor HOX13 resulting in de-regulation of the cell cycle as well as gemcitabine resistance (Wang et al., 2011;Li et al., 2015e).

Down-regulation of lncRNA LOC285194 in oesophageal cancer results in resistance to chemoradiotherapy (radiation in combination with platinum- or paclitaxel-based

chemotherapy) by influencing cell-cycle progression and non-apoptotic cell death pathway via regulating VEGF receptor 1 (Tong et al., 2014).

In contrast, lncRNA MALAT-1 is strongly over-expressed in oesophageal tumour tissue and binds miR-107 and miR-217 (Lin and Xu, 2015;Wang et al., 2015c). MiR-107 and miR-217 decoy translates in reduced activity of the ATM-CHK2 signalling pathway leading to reduced cell-cycle arrest and cell death as response to DNA damage (Smith et al., 2010;Wang et al., 2015c) and over-expression of the transcription factor B-Myb – an important regulator for G1/S and G2/M cell-cycle progression and cell survival (Lin and Xu, 2015;Wang et al., 2015c).

In addition, several microRNAs have been identified as regulators for cell cycle progression and induction of cell death pathways. Therefore, deregulated microRNA expression pattern is often a reason for drug resistance in GI tumours.

Colorectal cancers with up-regulated mir-203 are resistant to oxaliplatin (Zhou et al., 2014). Failure of oxaliplatin therapy is caused by miR-203 mediated down-regulation of the important mediator protein for DNA damage response ATM (Zhou et al., 2014). As reaction to DNA damage, ATM induces the expression of DNA repair proteins, interrupts the cell cycle and induces cell death in the case of extended DNA damage (Choy and Watters, 2018). Oxaliplatin resistance can also be caused by up-regulation of miR-503-5p in colorectal cancer (Xu et al., 2017a). Increased expression of miR-503-5p results in down-regulation of the apoptotic protein PUMA (p53 upregulated modulator of apoptosis) and leads to resistance to oxaliplatin-induced apoptosis (Xu et al., 2017a). In colon cancer tissues down-regulation of miR-320 is linked to resistance to 5-fluorouracil therapy (Wan et al., 2015). Among the targets for miR-320 is the transcription factor SOX4 which is involved in inhibition of p53-mediated apoptosis as well as the cell cycle regulators FOXM1 and FOXQ1 both known to have oncogenic potential (Wan et al., 2015;Vishnubalaji et al., 2016).

In colorectal cancer cells miR-21 over-expression results in inhibition of the MMR proteins MSH2 and MSH6, two important proteins for DNA damage recognition and repair (Valeri et al., 2010a). Inhibition of MSH2 and MSH6 leads to reduced G2/M cell-cycle arrest caused by 5-fluorouracil induced DNA damage and lower apoptosis rate *in-vitro* and *in-vivo* (Valeri et al., 2010a). Therefore, miR-21 over-expression reduces the therapeutic efficacy of 5-fluorouracil-based chemotherapy in colorectal cancer treatment (Valeri et al., 2010a).

Furthermore, it was proven that the core mismatch repair proteins MSH2, MSH6 and MLH1 are also down-regulated by miR-155 potentially contributing to drug resistance (Valeri et al., 2010b). According to another study, 5-fluorouracil resistance in colorectal cancer cells can also be mediated by increased expression of miR-31 causing cell cycle deregulation and reduced apoptosis rate (Wang et al., 2010b;Cekaite et al., 2012). Efficacy of 5-fluorouracil treatment in colorectal cancer patients can also be limited due to up-regulation of anti-apoptotic proteins like XIAP (X-linked inhibitor of apoptosis) and UBE2N (ubiquitin-conjugating enzyme E2N) as a consequence of decreased miR-96 expression (Kim et al., 2015) or due to up-regulation of the anti-apoptotic proteins Bcl-2, Bcl-2-like protein 11 (BIM) or Bcl-2-like protein 2 (Bcl2L2) by reduced expression of miR-129, miR-10b or miR-195, respectively (Nishida et al., 2012;Karaayvaz et al., 2013;Qu et al., 2015). In other colon cancer studies reduced expression levels of miR-365, miR-1915 and miR-34a have been described as reason for increased expression of BCL-2 (Wang et al., 2010a;Nie et al., 2012;Xu et al., 2013).

Increased Bcl-2 expression has been identified as a reason for resistance to 5-fluorouracil in other GI tumours, too, but the posttranscriptional regulation of mRNA coding for Bcl-2 is under the control of different miRNAs; *e.g.* in gastric cancer diminished expression of miR-204 is the reason (Sacconi et al., 2012). According to another study up-regulation of Bcl-2 is caused by lower miR-15b and miR-16 expression level and leads to drug resistance in gastric cancer cells due to reduced apoptosis (Xia et al., 2008). MiR-25 over-expression was related to cisplatin resistance in gastric cancer cells (He et al., 2017). MiR-25 targets directly mRNAs coding for tumour suppressors like FOXO3a, ERBB2, FBXW7 (Zhao et al., 2014a;Gong et al., 2015;Li et al., 2015a;He et al., 2017). All these proteins are involved in cell cycle regulation and apoptosis (Huang and Tindall, 2006;Nho and Hergert, 2014;He et al., 2017). Up-regulation of miR-223 targets FBXW7 (F-box/WD repeat-containing protein 7) and leads to cell-cycle deregulation and cisplatin resistance in gastric tumours (Zhou et al., 2015). Furthermore, up-regulation of miR-103/107 results in decreased expression of caveolin-1 in gastric cancer cells (Zhang et al., 2015d). The tumour suppressor caveolin-1 is a counter regulator for the Ras-p42/p44 MAP kinase pathway and due to the down-regulation by miR-103/107 increased activity of the Ras-p42/44 Map kinase pathway results in increased cell cycle progression and reduced cell death (Le Gall et al., 2000;Mebratu and Tesfaigzi, 2009). In gastric cancer increased cell cycle progression is also caused by

increased expression of miR-215 resulting in reduced expression of the tumour suppressor retinoblastoma 1, an important cell cycle regulator (Deng et al., 2014;Xu and Fan, 2015). Up-regulation of miR-106a targets FAS and inhibits the extrinsic apoptotic pathway in gastric cancer (Xiao et al., 2009;Wang et al., 2013c). In turn, reduced amount of FAS leads to increased cell proliferation, reduced apoptosis rate and drug resistance (Xiao et al., 2009;Wang et al., 2013c).

Over-expression of miR-21 inhibits cell cycle arrest resulting in increased cell proliferation, reduced apoptotic rate, gemcitabine and 5-fluorouracil resistance in pancreatic cancer (Moriyama et al., 2009;Park et al., 2009;Donahue et al., 2014). Similarly, in other pancreatic cancer studies, miR-21 over-expression results in reduced level of PTEN and Bcl-2 leading to activation of AKT-mTOR pathway, reduced apoptosis and resistance against gemcitabine treatment (Giovannetti et al., 2010;Dong et al., 2011). Increased expression of miR-214 represses directly ING4 in pancreatic tumour (Zhang et al., 2010). This impairs cell-cycle arrest, DNA repair as well as apoptosis and results in resistance to gemcitabine treatment (Zhang et al., 2010). The expression of the important pro-apoptotic protein BIM is reduced by miR-17-5p in pancreatic cancer and results in decreased apoptotic rate leading to resistance to gemcitabine treatment (Yan et al., 2012). Therapy failure is also caused by the repression of a tumour suppressor network involved in cell cycle and apoptosis regulation composed of PDCD4, BTG2 and NEDD4L by the combined action of miR-21, miR-23a and miR-27a (Frampton et al., 2014a;Frampton et al., 2014b). Furthermore, over-expression of miR-1246 results in decreased expression of cyclin-G2 and impairs the cell cycle regulation resulting in resistance to gemcitabine (Hasegawa et al., 2014). Recently miR-1307 was identified to be responsible for FOLFIRINOX resistance in pancreatic cancer (Carotenuto et al., 2018). MiR-1307 is up-regulated in *in-vitro* models of FOLFIRINOX resistant pancreatic cancer as well as in patient derived material compared to the surrounding tissue (Carotenuto et al., 2018). Reduced apoptosis rate and an extended acceptance of DNA damage seems to be the consequence of higher miR-1307 expression (Carotenuto et al., 2018).

In hepatocellular carcinoma the liver specific miR-122 is down-regulated and as consequence the expression of the target gene *CCNG1* is increased (Fornari et al., 2009). High level of cyclin G1 protein is found in several human tumours and results in reduced cell cycle control in the G2/M phase and modulation of p53 activity (Fornari et al., 2009;Xu et al., 2011). This

results in reduced DNA-repair and diminished apoptotic rate (Fornari et al., 2009;Xu et al., 2011). As already mentioned above, ABC transporter proteins are highly expressed in liver tumours due to the missing post-transcriptional regulator miR-122 (Xu et al., 2011). All these effects caused by miR-122 down-regulation promote doxorubicin resistance in liver cancer patients (Fornari et al., 2009;Xu et al., 2011). Another reason for doxorubicin resistance in liver cancer is based on reduced expression of miR-26b (Fan et al., 2008). Among the miR-26b targets in liver are the NF-κB activating proteins TAB3 and TAK1 (Fan et al., 2008;Zhao et al., 2014b). Therefore, a reduced expression of miR-26b results in increased activation of NF-κB and promotes drug resistance (Fan et al., 2008;Zhao et al., 2014b). Also, down-regulation of miR-101 is described as reason for resistance to doxorubicin in hepatocellular carcinoma (He et al., 2016). The anti-apoptotic protein Mcl-1 is among the targets of miR-101 and high levels of Mcl-1 renders liver tumour cells resistant to doxorubicin treatment (He et al., 2016). Furthermore, doxorubicin treatment failure in liver cancer patients has been connected to down-regulation of miR-199a-3p (Fornari et al., 2010). Besides targeting mTOR and c-Met, miR-199a-3p influences cell cycle regulation (Fornari et al., 2010). Decreased miR-199a-3p level results in down-regulation of the G1-checkpoint CDK inhibitors p21 (CDKN1A) and p27 (CDKN1B) and abrogate the G1 arrest following damage to DNA (Abukhdeir and Park, 2008;Fornari et al., 2010). In another study down-regulation of the G1 inhibitor CDKN1A in hepatocellular carcinoma was linked to up-regulation of miR-519d (Fornari et al., 2012). Consequently the apoptotic rate is reduced due to down-regulated miR-199a-3p as well as up-regulated miR-519d expression (Fornari et al., 2010;Fornari et al., 2012).

Another important tumour suppressor protein involved in resistance to anti-cancer drugs is PTEN because it is a main regulator for PI3K-AKT-mTOR pathway which is often hyperactivated in cancer and is one of the drivers for tumour growth and survival (Khan et al., 2013;LoRusso, 2016). PTEN itself is regulated by different microRNAs in different GI tumours, *e.g.*by miR-21 in liver and gastric cancer, miR-22 in p53-mutated colon cancer and mir-17-5p in colorectal cancer (Meng et al., 2007;Li et al., 2011;Zhang et al., 2012;Yang et al., 2013a;Fang et al., 2014). In all cases up-regulation of microRNAs results in decreased PTEN level in the tumour cell and subsequent activation of AKT-mTOR pathways resulting

in resistance to cisplatin (gastric cancer), paclitaxel (p53-mutated colon tumour) and FOLFOX (colorectal cancer) (Meng et al., 2007;Li et al., 2011;Zhang et al., 2012;Yang et al., 2013a;Fang et al., 2014). Down-regulation of PTEN due to over-expression of miR-19a and miR-19b in gastric cancer results in multi-drug resistance (Wang et al., 2013a).

Furthermore, mTOR is an important regulator under physiological as well as pathological conditions. In p53 mutant colorectal cancer mTOR is down-regulated by miR-338-3p and results in resistance to 5-fluorouracil treatment (Han et al., 2017). Indeed, inhibition of miR-338-3p in cell culture models restored sensitivity to 5-fluorouracil (Han et al., 2017) likely due to increased autophagy and reduced apoptosis following decrease in mTOR expression (Gonzalez et al., 2014;Han et al., 2017).

Autophagy is a further mechanism for chemoresistance (Song et al., 2009;Huang et al., 2016;Gozuacik et al., 2017;Xiong et al., 2017). In liver cancer up-regulation of lncRNA HULC activates autophagy by increasing the expression of ubiquitin-specific peptidase 22 (USP22) which in turn prevents the ubiquitin-mediated degradation of silent information regulator 1 (SIRT1) by removing the conjugated polyubiquitin chains from SIRT1 (Xiong et al., 2017). Autophagy causes resistance to oxaliplatin, 5-fluorouracil and epitubicin treatments in liver tumours (Xiong et al., 2017). In addition, lncRNA HULC down-regulates the expression of microRNAs that target directly the 3´-UTR of USP22 (miR-6825-5p, miR-6845-5p and miR-6886-3p) in liver cancer cells and prevents by this inhibition of USP22 at translational level (Xiong et al., 2017).

LncRNA MALAT-1 is highly expressed in gastric cancer cells resistant to 5-fluoruracil and cis-platin, respectively, compared to parental gastric cancer cells (YiRen et al., 2017). LncRNA MALAT-1 quenches miR-23b-3p and subsequently increases the expression of ATG12, an important regulator of autophagy (YiRen et al., 2017).

In oxaliplatin resistant colon cancer miR-409-3p is down-regulated so that the direct target Beclin-1 is expressed and induces autophagy (Tan et al., 2016). Over-expression of miR-409-3p results in low autophagic activity and overcomes oxaliplatin resistance in model systems of colon cancer (Tan et al., 2016).

Induction of epithelial-mesenchymal transition

Drug resistance can be caused by epithelial-mesenchymal transition (EMT) (Bedi et al., 2014;Heery et al., 2017). Several EMT-related signalling pathways are well known to be involved in mediating drug resistance in tumours (Nurwidya et al., 2012;Housman et al., 2014;Du and Shim, 2016;Heery et al., 2017). Cells undergoing EMT have several features in common with cancer stem cells (*e.g.* increased drug efflux pumps and anti-apoptotic effects) and furthermore EMT is instrumental for generation and maintenance of cancer stem cells (Housman et al., 2014;Du and Shim, 2016;Heery et al., 2017).

The lncRNA PVT1 (plasmacytoma variant translocation 1) has been found to be elevated in nearly all GI tumours including gastric, oesophageal, pancreatic, colon and liver cancers (Zheng et al., 2016;Wu et al., 2017;Zeng et al., 2017;Zhou et al., 2017). Increased expression of lncRNA PVT1 results in EMT and drug resistance (Zheng et al., 2016;Wu et al., 2017;Zhou et al., 2017).

The tumour suppressor lncRNA LEIGC prevents normal cells to undergo EMT. Therefore, the reduced expression of lncRNA LEIGC in gastric cancer fosters EMT and results in resistance to 5-fluorouracil treatment (Han et al., 2014b;Fang et al., 2015).

Up-regulation of lncRNA HULC has been correlated to induced EMT and suppressed apoptosis in gastric tumours leading to cisplatin resistance (Zhao et al., 2014c;Zhang et al., 2016b).

Increased expression of lncRNA-ATB (lncRNA-activated by TGF-β) in liver cancer results in competition with members of the miR-200 family for binding sites in the 3´-UTR of mRNAs coding for the transcription factors ZEB1 and ZEB2 (Yuan et al., 2014). In turn, high expression of ZEB1 and ZEB2 causes EMT and increased drug resistance (Yuan et al., 2014).

In pancreatic cancer the lncRNA MALAT-1 is a regulator of EMT (Ying et al., 2012;Jiao et al., 2014). In addition, the lncRNA MALAT-1 suppress G2/M cell cycle arrest and apoptosis leading to resistance to gemcitabine treatment (Jiao et al., 2014). As demonstrated by this example, the same lncRNA can induce resistance to chemotherapy by regulating different mechanisms at the same time.

Induction of EMT and resistance to gemcitabine treatment in pancreatic cancer cells can also be caused by miR-223 over-expression (Ma et al., 2015). Inhibition of miR-223 restored the

sensitivity of pancreatic cancer cell lines to gemcitabine treatment (Ma et al., 2015). Similarly, gemcitabine resistance in pancreatic cancer can also be caused by down-regulation of microRNAs as demonstrated for miR-200 (miR-200a, miR-200b and miR-200c) and let-7 family resulting in EMT (Li et al., 2009;Yu et al., 2010).

In colon cancer cells down-regulation of miR-147 results in EMT and increases the phosphorylation rate of AKT (Lee et al., 2014). Beside the activation of the PI3K-AKT pathway, the lower expression level of miR-147 also activates the TGF-β pathway and eventually leads to resistance to gefitinib treatment (Lee et al., 2014). Increased expression of miR-224 in colon cancer tissue was identified as another reason for resistance to 5-fluorouracil treatment. Increased miR-224 expression translates in increasing phosphorylation rate of extracellular signal-regulated kinase (ERK) and AKT, resulting in activation of both pathways (Amankwatia et al., 2015). In addition, miR-224 seems to activate also EGFR dependent- and NF-κB-signalling pathway leading to EMT (Amankwatia et al., 2015).

Cancer cell stemness

A further reason for drug resistance is the presence of cancer stem cells. Cancer stem cells are well known for being refractory to chemotherapies and therefore cause therapy failure and tumour recurrence or progression (Reya et al., 2001;Ischenko et al., 2010;Li et al., 2010;Shankar et al., 2011;Srivastava et al., 2011;Nguyen et al., 2012;Pattabiraman and Weinberg, 2014). Once again non-coding RNAs especially lncRNAs and microRNAs are involved in sustaining the cancer stem cell niche (Tay et al., 2008;Liu and Tang, 2011;Sun et al., 2014;Garg, 2015;Chen et al., 2017).

The lncRNA UCA1 (urothelial carcinoma associated 1; identical with lncRNA CUDR (cancer up-regulated drug resistant)) is strongly expressed in different tumours; among these, gastric, hepatocellular, pancreatic, colorectal cancers and oesophageal squamous cell carcinoma (Han et al., 2014a;Li et al., 2014b;Wang et al., 2015a;Chen et al., 2016;Shang et al., 2016;Chen et al., 2017;Li et al., 2017;Wang et al., 2017). LncRNA UCA1 binds to several microRNAs in different tumours (e.g. miR-216b in liver cancer, miR-204 in oesophageal and colon cancer, miR-27b in gastric cancer) and influences entire transcriptional programs as well as response towards therapy (Wang et al., 2015a;Bian et al.,

2016;Fang et al., 2016b;Jiao et al., 2016;Wang et al., 2017). Well-established up-regulated targets of lncRNA UCA1 are members of the Wnt-ß-catenin signalling pathway, several transcription factors and cell division regulators (Wang et al., 2008;Li and Chen, 2016). For cell stem cells the Wnt-ß-catenin pathway is of pivotal importance for cell self-renewal and mediating drug resistance (Taipale and Beachy, 2001;Fan et al., 2014a). Over-expression of lncRNA UCA1 results in resistance to cancer treatments with tamoxifen, 5-fluorouracil, gemcitabine, cisplatinum, doxorubicin, imatinib and tyrosine-kinase inhibitors targeting EGFR (Bian et al., 2016;Shang et al., 2016;Li et al., 2017;Wang et al., 2017).

Silencing of lncRNA UCA1 in *in-vitro* and *in-vivo* systems proved the oncogenic role of lncRNA UCA1 in gastric cancer (Shang et al., 2016;Li et al., 2017). Reduced expression level of lncRNA UCA1 results in reduced proliferation rate, increased apoptosis rate and overcomes the resistance to doxorubicin (Shang et al., 2016;Li et al., 2017). Furthermore, lncRNA UCA1 is a direct regulator of the PI3K-AKT-mTOR pathway (Li et al., 2017) which is often found to be deregulated in human cancers and is known to contribute to chemo-resistance of cancer cells (Xia and Xu, 2015;Safa, 2016). In another study over-expression of lncRNA UCA1 was shown to cause reduced miR-27 expression causing diminished apoptosis of gastric cancer cells due to increased Bcl-2 protein level in combination with reduced cleaved caspase-3 (Fang et al., 2016b). This results in multidrug resistance of gastric tumours (Fang et al., 2016b).

Over-expression of lncRNA UCA1 is also a reason for chemo-resistance against 5-fluorouracil treatment in colon cancer (Bian et al., 2016). LncRNA UCA1 causes resistance by binding miR-204-5p and consequently up-regulating the expression of its target genes Bcl-2, RAB22A and CREB1 (Bian et al., 2016). MiR-21 was identified as an important player in regard to failure of 5-fluorouracil therapy in colon cancer patients (Yu et al., 2013). Mir-21 is able to increase the number of undifferentiated cancer stem cells during 5-fluorouracil treatment and contributes by this to therapy failure (Yu et al., 2013).

In liver cancer lncRNA UCA1 contributes to chemotherapy resistance and malignant transformation of hepatocyte-stem cells (Gui et al., 2015;Li and Chen, 2016;Li et al., 2016a;Chen et al., 2017;Huang et al., 2017;Zheng et al., 2017). LncRNA UCA1 increases directly the transcription rate of the oncogene c-myc well known to be involved in drug resistance as well as in activating stem-cell like properties in hepatocarcinoma (Walker et al.,

1996;Lin et al., 2007;Pyndiah et al., 2011;Akita et al., 2014;Pu et al., 2015). Furthermore, lncRNA UCA1 also induces the expression of lncRNA HULC (highly up-regulated in liver cancer) in liver cancer and lncRNA HULC in turn stimulates the activity of the Wnt-ß-catenin pathway (Gui et al., 2015). In addition, lncRNA UCA1 forms a complex with the cell-cycle regulator cyclin-D which enhances the expression of lncRNA H19 by inhibiting the methylation of the lncRNA H19 promoter (Pu et al., 2015;Chen et al., 2017). High level of lncRNA H19 induces the telomerase activity and enhances the length of telomere thereby supporting the stem cell properties (Hiyama and Hiyama, 2007;Pu et al., 2015;Wu et al., 2016b). Another effect of lncRNA UCA1 is the enhanced phosphorylation of the tumour suppressor retinoblastoma protein 1(RB1). RB1 phosphorylation results in increased cell cycle progression and in interaction of the phosphorylated retinoblastoma protein 1 with the SET1A complex. Such interaction catalyses the transcription-activating methylation of histone H3 lysine-4 on several gene promoters including telomeric repeat-binding factor 2 promoter an important component for the telomerase extension process (Fang et al., 2016a;Li et al., 2016a).

In liver cancer as well as in pancreatic, gastric, oesophageal and colon cancers a critical role in inducing the transformation of stem cells into cancer stem cell has been demonstrated for lncRNA HOTAIR (Chen et al., 2013;Endo et al., 2013;Kim et al., 2013;He et al., 2014;Mohamadkhani, 2014;Li et al., 2015b;Chen et al., 2017). LncRNA HOTAIR is a strong activator for expression of *OCT4*, *RNF51*, *CD44* and *CD133* genes – all these proteins are involved in reprogramming the gene network to acquire cancer stem cell properties (Padua Alves et al., 2013;Zhu et al., 2014). LncRNA HOTAIR expression causes resistance against cisplatin and doxorubicin treatment in liver cancer model systems (Yang et al., 2011) and renders gastric tumours resistant to cisplatin therapy by binding miR-126 and activating the PI3K-AKT-mTOR pathway (Yan et al., 2016). In the context of several GI cancer stem cells it has been shown that lncRNA HOTAIR down-regulates the expression of histone methyltransferase SETD2 and reduces the phosphorylation rate of SETD2 resulting in reduced trimethylation of histone H3 lysine-36 on several gene promoter, *e.g.* Wnt inhibitory factor-1 (WIF-1) (Ge et al., 2013;Kim et al., 2013;Ding et al., 2014;Li et al., 2015b). Reduced WIF-1 expression leads to activation and increased signalling through the Wnt-ß-catenin pathway (Ge et al., 2013;Kim et al., 2013). Furthermore, the modulated chromatin organisation account for a reduced efficiency of the mismatch repair system and damaged

DNA can escape from corrections leading to microsatellite instability (MSI) and altered expression of cell cycle regulators as well as reduced apoptosis (Gupta et al., 2010;Valeri et al., 2010b;Chen et al., 2013;Li et al., 2013;Li et al., 2015b). In addition, lncRNA HOTAIR induces accumulation of replication errors by hindering the complex formation of MSH2 with MSH6; one essential dimer for DNA mismatch recognition and repair (Yang et al., 2004;Valeri et al., 2010a;Valeri et al., 2010b;Edelbrock et al., 2013;Pfister et al., 2014).

In pancreatic cancer the oncogenic lncRNA MALAT-1 (metastasis-associated lung adenocarcinoma transcript-1) contributes to the expression of the cancer stem cell marker CD133, CD44, CD24 and aldehyde-dehydrogenase (Fan et al., 2014b;Jiao et al., 2014;Jiao et al., 2015). In addition, the expression of the core pluripotent factors OCT4, NANOG and SOX2 are also under the control of lncRNA MALAT-1 (Jiao et al., 2015). LncRNA linc-ROR inhibits the expression of p53 and activates by this the transcription factor ZEB1 in pancreatic cancer (Wellner et al., 2009). ZEB1 in turn suppress the expression of the miR-200 family that leads to maintenance of pancreatic cancer stemness and induces EMT known to be responsible for paclitaxel resistance in pancreatic cancer patients (Wellner et al., 2009;Kim, 2017). Down-regulation of miR-205 results in increased expression of stem cell markers OKT3, OKT8 and CD44 in pancreatic cancer tissue and is linked to gemcitabine resistance (Singh et al., 2013). Re-expression of miR-205 is able to overcome the gemcitabine resistance in pancreatic cancer model systems (Singh et al., 2013).

The lncRNA-34a mediates an increase in self-renewal of colon cancer stem cells and induce Wnt as well as NOTCH signalling pathways via sequester miR-34a expression (Bu et al., 2013;Evans et al., 2015).

In hepatocellular carcinoma the lncRNA linc-ROR (long intergenic ncRNA regulator of reprogramming) is involved in regulating core pluripotent factors (OCT-4, NANOG, SOX2) necessary for the stem cell like phenotype and causes resistance to chemotherapy (Takahashi et al., 2014). LncRNA linc-ROR competes with miR-145 for the same binding sites present in the mRNAs coding for OCT-4, NANOG and SOX2 (Wang et al., 2013b). Presence of lncRNA linc-ROR prevents the binding of miR-145 to the mRNA of the core pluripotent factors resulting in translation of these mRNAs and maintains the stem cell phenotype (Wang et al., 2013b). Furthermore, the expression of CD133, another cancer stem cell marker, is directly induced by lncRNA linc-ROR (Takahashi et al., 2014).

MiR-130b is connected to cancer stem cells growth in liver tumours (Ma et al., 2010). Increased expression of miR-130b targets directly the mRNA coding for tumour protein 53-induced nuclear protein 1 and reduces the expression level of the corresponding protein (Ma et al., 2010). Furthermore, high level of miR-130b renders liver tumour cells resistant to doxorubicin treatment (Ma et al., 2010). Another reason for doxorubicin resistance in liver cancer patients is down-regulation of the tumour suppressor miR-101 resulting in increased protein expression of enhancer of zeste homolog 2 (EZH2) (Sasaki et al., 2008;Xu et al., 2014a). EZH2 is a histone-lysine N-methyltransferase enzyme that silence Wnt-pathway antagonists and other tumour suppressor genes on the transcriptional level by histone methylation (Cheng et al., 2011). Over-expression of EZH2 is positively correlated with increased Wnt-ß-catenin signalling (Cheng et al., 2011).

MiR-221 is over-expressed in 5-fluorouracil resistant oesophageal tumours (Wang et al., 2016b). The mechanisms of resistance is mediated via down-regulation of the direct target DDK2 (dickkopf-related protein 2) and subsequent activation of the Wnt-ß-catenin pathway (Wang et al., 2016b). Furthermore, increased miR-221 expression fosters EMT and facilitates the formation of tumour stem cells (Wang et al., 2016b).

In colon cancer stem cells, miR-451 was found to be down-regulated compared to colon cancer cells (Bitarte et al., 2011). Reduced level of miR-451 seems to be essential for the self-renewal of colon cancer stem cells (Bitarte et al., 2011). In addition, expression of ABCB1 transporter is increased in colon cancer stem cells due to lack of miR-451 post-transcriptional down-regulation resulting in resistance to irinotecan treatment (Bitarte et al., 2011).

MiR-1182 is often down-regulated in gastric cancer tissue (Zhang et al., 2015a). One direct target of miR-1182 is telomerase reverse transcriptase (hTERT), an enzyme that is involved in controlling the length of telomere. Over-expression of hTERT due to missing transcriptional regulation by miR-1182, results in cell immortality and stem-cell property of gastric cancer cells (Zhang et al., 2015a).

Targeted therapies and drug resistance

For GI cancer several targeted therapies exist (Table 3) (Jonker et al., 2007;Weber and McCormack, 2008;Loupakis et al., 2010;Roukos, 2010;Grothey et al., 2013;Muro et al., 2015;King et al., 2017). They are used alone or in combination with chemotherapy. Unfortunately in most cases the patients develop resistance also against these targeted therapies and the above outlined general principles of drug resistance based on non-coding RNA dysregulation are involved. Beside that non-coding RNAs interfering with the targeted protein itself or (up-)regulating the targeted signal pathway are involved in drug resistance (Roukos, 2010). Furthermore, therapy failure can be related to activation of alternative signal pathways by non-coding RNAs (Roukos, 2010;Lu et al., 2017b).

Recently it was demonstrated that resistance to cetuximab in colon cancer patients and in *in-vitro* 3-D-cell culture models can be caused by over-expression of lncRNA MIR100HG (Lu et al., 2017b). Two microRNAs, miR-100 and miR-125b, are generated from lncRNA MIR100HG and these microRNAs down-regulate in a concerted way five negative regulators of the Wnt/ß-catenin pathway resulting in increased Wnt signalling (Lu et al., 2017b). This kind of cetuximab resistance can be overcome by inhibition of Wnt signalling, underscoring the potential clinical relevance of the interactions between EGFR and Wnt/ß-catenin pathways (Lu et al., 2017b). Increased mir-125b expression is also correlated with trastuzumab resistance in HER2-positive gastric cancer patients but up to now the molecular basis for this resistance is unclear (Sui et al., 2017). Sorafenib resistance in hepatocellular carcinoma is caused by lncRNA TUC338 (Jin et al., 2017). RASAL-1 (RAS protein activator like-1) is a direct target of lncRNA TUC338 and high expression of lncRNA TUC338 inhibits the RASAL-1 expression resulting in activation of RAS-signalling (Jin et al., 2017). According to another *in-vitro* study, reduced expression of miR-193b leads to higher expression of the anti-apoptotic protein Mcl-1 and renders hepatocellular carcinoma cells resistant to sorafenib treatment (Braconi et al., 2010).

Non-coding RNAs as potential biomarkers of resistance and novel therapeutics: promises and hurdles

Our review summarises most of the current evidence supporting the role of non-coding RNAs in resistance to chemotherapy and targeted agents. It is likely that, in the near future, given the promising and exciting results obtained with the use of immunotherapy in

gastroesophageal (Kang et al., 2017) and colorectal cancer (Le et al., 2017;Overman et al., 2018), new data will emerge on the already known regulation of PD-1, PD-L1 and CTLA-4 by non-coding RNAs and response to nivolumab and pembrolizumab (Cortez et al., 2016;Xu et al., 2016;Smolle et al., 2017).

The contribution of non-cording RNAs in resistance mechanisms to a broad range of anti-cancer treatments makes their use as biomarkers or novel therapeutics quite promising but several challenges remain.

Given microRNAs and, to a lesser extent, other non-coding RNAs can be reliably detected in tissues and bio-fluids such as plasma, serum and urine, it is tempting to hypothesize the use of non-coding RNA based tools to predict and monitor resistance to anticancer treatments. Few studies have already tested the validity of microRNAs as biomarkers of response to anticancer treatment in other cancers such as prostate (Lin et al., 2017), chronic lymphocytic leukaemia (Gagez et al., 2017) and sarcomas (Wiemer et al., 2017). In colorectal cancer, we (Sclafani et al., 2015) and others (Graziano et al., 2010;Zhang et al., 2011;Sha et al., 2014) have tested the contribution of a single nucleotide polymorphism (SNP) in the binding site of let-7 in the *KRAS* 3'UTR in predicting benefit from anti-EGFR treatment with conflicting results across different trials. Despite the good reproducibility of the assay, the predictive value of the test was not confirmed in all trials likely due to use of cetuximab in different context (neo-adjuvant, adjuvant and metastatic colorectal cancer, respectively). Similarly the analysis of a SNP in miR-608 led to contradicting results in patients treated with neo-adjuvant or adjuvant chemo- and radiochemo-therapy in colon and rectal cancers highlighting some of the challenges in validating data obtained in retrospective series (Lin et al., 2012;Xing et al., 2012;Pardini et al., 2015;Sclafani et al., 2016). Tissue (cancer *versus* stroma) and organ (colon *versus* rectum) specificity in non-coding RNA expression might represent potential explanations for different findings obtained in some of these studies. Beside SNPs, expression of microRNAs can be detected in fresh frozen or formalin fixed paraffin embedded tissues and serve as potential biomarker of sensitivity or resistance to treatment. Robust data have emerged from the retrospective analysis of a prospective phase III clinical trial (Laurent-Puig et al., 2016). In this study, *KRAS* wild-type patients were classified based on high or low miR-31-3p expression: patients with high expression were resistant to cetuximab while patient with low expression had good and durable responses

which translated in survival benefit. The miR-31 expression cut-off for the classification into high or low expression was predefined in the above study. However, one of the key challenges in validating these interesting findings will be design of a clinically approved assay that can accurately assign patients into one of these two categories. In this prospective, the use of different sources of material (i.e. primary colorectal cancer *versus* metastasis) might result in different basal expression of the microRNA and as such different scoring. Source of material and choice of reference controls represent important obstacles that might bias the definition of a threshold for high or low expression of microRNAs in tissues and bio-fluids. MicroRNAs can be detected in plasma, serum and urine samples and have been used for early detection and prognostic purposes in gastrointestinal cancer (Schultz et al., 2014;Shigeyasu et al., 2017;Ozawa et al., 2018). The use of digital droplet approaches allows the quantitative detection of copies of the microRNA of interest based on the starting volume of bio-fluids and, potentially overcomes or at least mitigates, the issues related to the normalization of data against reference controls, making the definition of cut-off easier to standardize. One study has reported the potential role of miR-126 in predicting and tracking response to chemotherapy and anti-VEGF treatment in colorectal cancer (Hansen et al., 2015) and, with the advent of digital quantitative technologies, more studies are expected.

In consideration of their role in cancer initiation, progression and resistance to treatment, non-coding RNAs and among them microRNAs have been proposed as potential therapeutics (Adams et al., 2017). A large body of pre-clinical evidence is available on the use of anti-microRNAs or molecules re-expressing microRNAs alone or in combination with other agents in order to increase efficacy and prevent or revert drug resistance (Rupaimoole and Slack, 2017). Inhibition of microRNAs has been tested in clinical trials in the context of HCV infection (Janssen et al., 2013;van der Ree et al., 2017) and in mesothelioma (van Zandwijk et al., 2017). These trials highlighted a huge potential for microRNA-based therapeutics but at the same time pinpointed some of the criticalities in further clinical development of such approaches. MiR-122 inhibition led to durable viral load reduction in both HCV trials and was associated with manageable side effects. Similarly, in mesothelioma patients treated with miR-16-loaded minicells the disease control rate was satisfactory and the toxicity profile acceptable warranting further investigations. Overall in both approaches the risk of off-target effects represent the main hurdle to be taken into account: indeed miR-122 inhibition has been associated with risk of developing liver cancer in pre-clinical models

(Hsu et al., 2012) and, similarly, over-expression of miR-16 might lead to uncontrolled cardiac effects as proven in the phase I trial (van Zandwijk et al., 2017). These effects might be increased in combination studies in which anti-microRNAs or microRNA-conjugates are delivered together with chemotherapy leading to cumulative side effects. Therefore a robust understanding of the biology underpinning microRNA deregulation in physiology and pathological conditions in order to implement effort that can minimise the risk of serious adverse events hampering the clinical development of microRNA-based strategies.

Conclusion:

Non-coding RNAs especially lncRNAs and microRNAs are important mediators for drug resistance. They function in an organ and tissue specific manner and through different molecular mechanisms. One non-coding RNA always have several targets and in the end deregulation of one non-coding RNA alters the expression level of several proteins in a tissue specific way. For example, in the case of miR-374b more than 700 genes have been identified as direct target in pancreatic tissue (Schreiber et al., 2016). Drug resistance is a dynamic process caused by several cell and non-cell autonomous mechanisms. Given non-coding RNAs can simultaneously control several cancer-associated pathways, non-coding RNA dysregulation plays a crucial role in treatment resistance. Future studies will continue to shed insights in the fine interplay among lncRNA, microRNA and their target genes and might provide opportunities for more effective strategies to prevent or overcome resistance. In the interim, given non-coding RNAs and especially microRNAs can be tested in tissues and biofluids in a rapid, cost/effective and robust way. More investigational studies should explore their utility to monitor and forecast treatment response and resistance in order to personalise treatments and improve patient's outcomes.

Conflict of Interest:

No conflicts to declare.

Author Contributions:

853 NV and JCH: idea, conception and writing the review.

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Figure legends:

Figure 1: Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in liver cancer. For details about target genes and regulated protein expression by the non-coding RNAs see text.

Figure 2: Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in oesophageal cancer. For details about target genes and regulated protein expression by the non-coding RNAs see text.

Figure 3: Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in gastric cancer. For details about target genes and regulated protein expression by the non-coding RNAs see text.

Figure 4: Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in colon and colorectal cancer. For details about target genes and regulated protein expression by the non-coding RNAs see text.

Figure 5: Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in pancreatic cancer. For details about target genes and regulated protein expression by the non-coding RNAs see text.

Figure 6: Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in gastrointestinal stromal cancer. For details about target genes and regulated protein expression by the non-coding RNAs see text.

Figure 7: Role of non-coding RNAs for the different reasons that can cause resistance to anticancer drugs in cholangiocarcinoma. For details about target genes and regulated protein expression by the non-coding RNAs see text.

878 **Table1: Overview about non-coding RNAs involved in resistance to anticancer drugs in**
879 **gastrointestinal tumours.**

880 Abbreviation used: GI=gastrointestinal; vRNA=vault RNA; lncRNA=long non-coding RNA;
881 miR=microRNA; EMT=epithelial-mesenchymal transition

882

Non-coding RNA	GI cancer type	Causing drug resistance via	Reference
lncRNA AK022798	gastric cancer	increasing the expression of *ABCB1* gene	(Hang et al., 2015)
lncRNA ANRIL	gastric cancer	increasing the expression of *MDR1* gene	(Zhang et al., 2015c;Lan et al., 2016)
lncRNA ARA	liver cancer	reduced G2/M cell-cycle arrest; reduced apoptosis rate; de-regulation of MAPK-pathway	(Jiang et al., 2014;Cox and Weinman, 2016)
lncRNA-ATB	liver cancer	increased expression of ZEB1 and ZEB2; induced EMT	(Yuan et al., 2014)
lncRNA CCAL	colorectal cancer	increasing the expression of *ABCB1* gene; increased activity of Wnt/ß-catenin pathway	(Ma et al., 2016b)
lncRNA H19	liver cancer oesophageal cancer	up-regulation of membrane glycoprotein p95; elevating the expression of *MDR1* gene by increasing promoter methylation; increasing telomere length	(Hiyama and Hiyama, 2007;Tsang and Kwok, 2007;Matouk et al., 2013)
lncRNA HOTAIR	liver cancer colorectal cancer pancreatic cancer GI stromal tumour	increased expression of PRC2 complex members; genome-wide changes in transcription process due to epigenetic chromatin silencing; down-regulation of p21(WAF/CIP1); repression of G1/S cell-cycle arrest; increased proliferation rate; reduced DNA-damage response	(el-Deiry et al., 1993;Geng et al., 2011;Kogo et al., 2011;Liu et al., 2013)
lncRNA HOTAIR	colon cancer pancreatic cancer gastric cancer	transformation of stem cells into cancer stem cells due to activation of *OCT4, RNF51,*	(Yang et al., 2004;Edelbrock et al., 2013;Ge et al.,

	oesophageal cancer	*CD44* and *CD133* gene expression; increased activity of Wnt/ß-catenin pathway; modulation of chromatin organisation leads to reduced efficiency of the mismatch repair system; increased MSI; reduced apoptosis rate; inhibition of the expression of miR-126 and activating the PI3K-AKT-mTOR pathway (in gastric cancer)	2013;Kim et al., 2013;Padua Alves et al., 2013;Zhu et al., 2014;Yan et al., 2016)
lncRNA HOTTTIP	pancreatic cancer	increased expression of transcription factor HOX13; cell cycle deregulation	(Wang et al., 2011;Li et al., 2015e)
lncRNA HULC	liver cancer	increased activity of Wnt-ß-catenin; increased expression of USP22 and SIRT1; reduced expression of miR-6825-5p, miR-6845-5p, miR-6886-3p; increased autophagy pathway	(Xiong et al., 2017)
lncRNA HULC	gastric cancer	induced EMT; suppressed apoptosis	(Zhao et al., 2014c;Zhang et al., 2016b)
lncRNA LEIGG	gastric cancer	induced EMT	(Han et al., 2014b;Fang et al., 2015)
lncRNA linc-ROR	pancreatic cancer	inhibition of p53; inhibition of the expression of miR-200 family; increased expression of the transcription factor ZEB1; induced EMT	(Wellner et al., 2009;Kim, 2017)
lncRNA linc-ROR	liver cancer	preventing the binding of miR-145 to pluripotent factors OKT-4, NANOG and SOX2 resulting in increased expression of these transcription factors necessary for sustain stem cell character	(Wang et al., 2013b;Takahashi et al., 2014)
lncRNA LOC285194	oesophageal cancer	cell-cycle deregulation; blocking non-apoptotic cell death pathway	(Tong et al., 2014)

lncRNA MALAT-1	oesophageal tumour	binds miR-107 and miR-217; reduced activity of the ATM-CHK2 signalling pathway; reduced cell-cycle arrest and cell death as response to DNA damage; increased expression of transcription factor B-Myb	(Smith et al., 2010;Lin and Xu, 2015;Wang et al., 2015c)
lncRNA MALAT-1	pancreatic cancer	increased expression of cancer stem cell marker CD133; increased expression of pluripotent factors OCT4, NANOG and SOX2; induced EMT; repression of G2/M cell-cycle arrest; reduced apoptosis rate	(Ying et al., 2012;Jiao et al., 2014;Jiao et al., 2015)
lncRNA MALAT-1	gastric cancer	sequestering of miR-23b-3p; increased expression of ATG12; increased autophagy	(YiRen et al., 2017)
lncRNA MIR100HG	colon cancer	increased activity of Wnt-ß-catenin pathway	(Lu et al., 2017b)
lncRNA MRUL	gastric cancer	increasing the expression of *MDR1* gene	(Wang et al., 2014)
lncRNA PANDAR	gastric cancer colorectal cancer hepatocellular cancer cholangiocarcinoma	interacts with the transcription factor NF-YA resulting in reduced translation of pro-apoptotic genes – leading to reduced apoptosis rate and increased proliferation	(Hung et al., 2011;Peng and Fan, 2015;Ma et al., 2016a;Lu et al., 2017a;Xu et al., 2017b)
lncRNA PVT1	gastric cancer oesophageal cancer pancreatic cancer colon cancer liver cancer	induced EMT	(Zheng et al., 2016;Wu et al., 2017;Zhou et al., 2017)
lncRNA PVT-1	gastric cancer	increasing the expression of *MDR1* gene	(Zhang et al., 2015c;Lan et al., 2016)
lncRNA TUC338	hepatocellular cancer	inhibiting the RASAL-1 pathway	(Jin et al., 2017)
lncRNA TUG1	oesophageal cancer gastric cancer colorectal cancer hepatocellular cancer cholangiocarcinoma	increasing the expression of *Bc-2* gene; reducing the expression of cyclin-dependent protein kinase, caspase-3, caspase-9 and Bax; decreasing G0/G1 arrest during cell cycle; reducing apoptosis rate; inducing EMT	(Huang et al., 2015;Dong et al., 2016;Jiang et al., 2016;Li et al., 2016b;Wang et al., 2016a;Zhang et al., 2016a;Xu et al., 2017c)

lncRNA UCA1 (identical with lncRNA CDUR)	liver cancer colorectal cancer pancreatic cancer gastric cancer oesophageal cancer	sequestering microRNAs (miR-216b in liver cancer; miR-204-5p in colorectal and oesophageal cancer; miR-27 in gastric cancer); increase expression of lncRNAs (HULC; H19); increased activity of Wnt-ß-catenin pathway; increased activity of PI3K-AKT-mTOR pathway; increased phosphorylation of tumour suppressor retinoblastoma; increased expression of c-myc; increased cell-cycle progression; increased expression of anti-apoptotic protein Bcl-2; reduced expression of PARP (in gastric cancer); reduced apoptosis rate. In liver cancer additional effects: transformation of stem cells into cancer stem cells due to increased c-myc expression; increasing telomere length	(Walker et al., 1996;Hiyama and Hiyama, 2007;Wang et al., 2008;Gui et al., 2015;Pu et al., 2015;Bian et al., 2016;Fang et al., 2016a;Fang et al., 2016b;Li and Chen, 2016;Shang et al., 2016;Chen et al., 2017;Li et al., 2017)
lncRNA URHC	liver cancer	reduced expression of the tumour suppressor ZAK; increased proliferation rate; reduced apoptosis rate	(Xu et al., 2014b)
lncRNA-34a	colon cancer	increased activity of Wnt-ß-catenin pathway; increased activity of NOTCH pathway; increasing the self-renewal of cancer stem cells	(Bu et al., 2013;Evans et al., 2015)
miR let-7 family	pancreatic cancer	induced EMT	(Li et al., 2009)
miR let-7a	pancreatic tumours	increased expression of RRM2	(Bhutia et al., 2013)
miR let-7g	oesophageal cancer	increased expression of ABCC10	(Wu et al., 2016a)
miR let-7i	oesophageal cancer	increased expression of ABCC10	(Wu et al., 2016a)
miR-100	colon cancer	increased activity of Wnt-ß-catenin pathway	(Lu et al., 2017b)
miR-101	liver cancer	increased expression of EZH2; increased activity of Wnt-ß-catenin pathway; increased expression of Mcl-	(Sasaki et al., 2008;Xu et al., 2014a;He et al., 2016)

		1; reduced apoptosis rate	
miR-10b	colorectal cancer	increased expression of anti-apoptotic protein BIm	(Nishida et al., 2012)
miR-103/107	gastric cancer	reduced expression of tumour-suppressor caveolin-1; activation of Ras-p42/p44 MAP pathway; reduced apoptosis rate	(Le Gall et al., 2000;Mebratu and Tesfaigzi, 2009;Zhang et al., 2015d)
miR-106a	gastric cancer	reduced expression of FAS; reduced apoptosis rate	(Xiao et al., 2009;Wang et al., 2013c)
miR-1182	gastric cancer	increased expression of hTERT	(Zhang et al., 2015a)
miR-122	liver cancer	increased expression of ABC proteins; increased expression of cyclin G1; reduced G2/M cell-cycle arrest; reduced DNA repair; reduced apoptosis rate	(Fornari et al., 2009;Xu et al., 2011)
miR-124	pancreatic cancer liver cancer	reduced expression of SLC16A1	(Pullen et al., 2011)
miR-125b	colon cancer	increased activity of Wnt-ß-catenin pathway	(Lu et al., 2017b)
miR-1246	pancreatic cancer	reduced expression of cyclin-G2; de-regulated cell-cycle	(Hasegawa et al., 2014)
miR-129	colorectal cancer	increased expression of anti-apoptotic protein Bcl-2	(Karaayvaz et al., 2013)
miR-1291	pancreatic cancer	increased expression of ABCC1	(Pan et al., 2013)
miR-130b	liver cancer	reduce expression of tumour protein 53-induced nuclear protein 1	(Ma et al., 2010)
miR-1307	pancreatic cancer	reduced apoptosis rate	(Carotenuto et al., 2018)
miR-133a	oesophageal cancer	increased expression of GSTP1	(Kano et al., 2010)
miR-145	colon carcinoma	increased expression of ABCB1	(Ikemura et al., 2013)
miR-147	colon cancer	induced EMT; increased phosphorylation of AKT; increased activity of PI3K-AKT-mTOR pathway; increased activity of TGF-ß pathway	(Lee et al., 2014)

miR-155	colorectal cancer	inhibition of MSH2, MSH6 and MLH1	(Valeri et al., 2010b)
miR-15b	gastric cancer	increased expression of anti-apoptotic protein Bcl-2	(Xia et al., 2008)
miR-16	gastric cancer	increased expression of anti-apoptotic protein Bcl-2	(Xia et al., 2008)
mir-17-5p	colorectal cancer	reduced expression of PTEN expression; activation of AKT-mTOR pathways	(Fang et al., 2014)
miR-17-5p	pancreatic cancer	reduced expression of BIM	(Yan et al., 2012)
miR-1915	colon cancer	increased expression of BCL-2	(Xu et al., 2013)
miR-192	colon cancer	reduced expression of thymidylate synthase; altered cell-cycle control at multiple levels; prevent progression into the S-phase	(Boni et al., 2010)
miR-193b	hepatocellular cancer	increased expression of Mcl-1	(Braconi et al., 2010)
miR-195	colorectal cancer	increased expression of anti-apoptotic protein Bcl-2L2	(Qu et al., 2015)
miR-199a-3p	liver cancer	reduced G1/S cell-cycle arrest; increased expression of mTOR and c-Met; reduced apoptosis rate	(Abukhdeir and Park, 2008;Fornari et al., 2010)
miR-19a	gastric cancer	reduced expression of PTEN expression; activation of AKT-mTOR pathways	(Wang et al., 2013a)
miR-19b	gastric cancer	reduced expression of PTEN expression; activation of AKT-mTOR pathways	(Wang et al., 2013a)
miR-200a	pancreatic cancer	induced EMT	(Li et al., 2009)
miR-200b	pancreatic cancer	induced EMT	(Li et al., 2009)
miR-200c	pancreatic cancer	induced EMT	(Li et al., 2009;Yu et al., 2010)
miR-203	colorectal cancer	reduced expression of ATM; impaired DNA repair; reduced apoptosis rate	(Zhou et al., 2014)
miR-205	pancreatic cancer	increased expression of pluripotent factors OKT3, OKT8 and CD44	(Singh et al., 2013)
miR-21	colorectal cancer	inhibition of MSH2 and MSH6; reduced G2/M cell-cycle arrest; reduced apoptosis rate; increasing the number of undifferentiated cancer stem cells	(Valeri et al., 2010a;Yu et al., 2013)

miR-21	pancreatic cancer	reduced cell-cycle arrest; reduced expression of PTEN; activation of AKT-mTOR pathway; increased expression of anti-apoptotic protein Bcl-2; increased cell proliferation; reduced apoptosis rate	(Giovannetti et al., 2010;Dong et al., 2011)
miR-21	liver cancer gastric cancer	reduced expression of PTEN expression; activation of AKT-mTOR pathways	(Meng et al., 2007;Zhang et al., 2012;Yang et al., 2013a)
synergistic action of miR-21 miR-23a miR-27a	pancreatic cancer	reduced expression of the tumour suppressors PDCD4, BTG2 and NEDD4L; de-regulated cell-cycle; reduced apoptosis rate	(Frampton et al., 2014a;Frampton et al., 2014b)
miR-211	pancreatic tumours	increased expression of RRM2	(Maftouh et al., 2014)
miR-215	liver cancer	reduced expression of dihydrofolate reductase; reduced expression of thymidylate synthase	(Wang et al., 2015b)
miR-215	colon cancer	reduced expression of thymidylate synthase; altered cell-cycle control at multiple levels; prevent progression into the S-phase	(Boni et al., 2010)
miR-215	gastric cancer	reduced expression of retinoblastoma 1; altered cell-cycle control	(Deng et al., 2014;Xu and Fan, 2015)
miR-22	p53-mutated colon cancer	reduced expression of PTEN expression; activation of AKT-mTOR pathways	
miR-221	oesophageal cancer	reduced expression of DDK2; activation of Wnt/ß-catenin pathway; induced EMT	(Li et al., 2011;Wang et al., 2016b)
miR-223	liver cancer	increased expression of ABCB1	
miR-223	pancreatic cancer	induced EMT	(Ma et al., 2015)
miR-223	gastric cancer	reduced expression of FBXW7; altered cell-cycle control	(Zhou et al., 2015)
miR-224	colon cancer	induced EMT; increased phosphorylation of AKT und ERK; increased activity of PI3K-AKT-mTOR pathway; increased activity of ERK	(Amankwatia et al., 2015)

		pathway; activation of NF-æB and EGFR dependent pathways	
miR-23a	microsatellite instable colon cancer	increased expression of ABCF1	(Li et al., 2015c)
miR-25	gastric cancer	reduced expression of FOXO3a, ERBB2 and FBXW7; cell-cycle deregulation; reduced apoptosis rate	(Zhao et al., 2014a;Gong et al., 2015;Li et al., 2015a;He et al., 2017)
miR-26b	liver cancer	increased activation of NF-æB	(Fan et al., 2008;Zhao et al., 2014b)
miR-27a	liver cancer	reduced expression of dihydropyrimidine dehydrogenase	(Offer et al., 2014)
miR-27b	liver cancer	increased expression of CYP1B1; reduced expression of dihydropyrimidine dehydrogenase	(Offer et al., 2014;An et al., 2017)
miR-27b	pancreatic cancer	reduced expression of CYP3A4– resulting in cyclophosphamide resistance due to missing drug activation	(Pan et al., 2009)
miR-297	colorectal cancer	increased expression of ABCC2	(Xu et al., 2012)
miR-29a	pancreatic cancer liver cancer	reduced expression of SLC16A1	(Pullen et al., 2011)
miR-29b	pancreatic cancer liver cancer	reduced expression of SLC16A1	(Pullen et al., 2011)
miR-31	colorectal cancer	cell-cycle deregulation; reduced apoptosis rate	(Wang et al., 2010b;Cekaite et al., 2012)
miR-320	colon cancer	increased expression of SOX4; inhibition of p53 mediated apoptosis; reduced expression of FOXM1 and FOXQ1; cell-cycle deregulation	(Wan et al., 2015;Vishnubalaji et al., 2016)
miR-338-3p	p53 mutant colorectal cancer	reduced expression of mTOR; increased autophagy and reduced apoptosis rate	(Han et al., 2017)
miR-34a	colon cancer	increased expression of anti-apoptotic protein Bcl-2	(Wang et al., 2010a)
miR-365	colon cancer	increased expression of anti-apoptotic protein Bcl-2	(Nie et al., 2012)

miR-374b	pancreatic cancer	increased ATP7A expression	(Schreiber et al., 2016)
miR-378	liver cancer	increased expression of CYP2E1	(Mohri et al., 2010)
miR-409-3p	colon cancer	increased expression of Beclin-1; increased autophagy pathway	(Tan et al., 2016)
miR-451	colon cancer	increasing the self-renewal of cancer stem cells; increased expression of ABCB1	(Bitarte et al., 2011)
miR-494	colon cancer	reduced expression of dihydropyrimidine dehydrogenase	(Chai et al., 2015)
miR-503-5p	colorectal cancer	reduced expression of apoptotic protein PUMA	(Xu et al., 2017a)
miR-508-5p	gastric cancer	increased expression of ABCB1; increased expression of transcription factor ZNRD1	(Shang et al., 2014)
miR-519d	liver cancer	reduced expression of G1-checkpoint CDK inhibitor p21; reduced apoptosis rate	(Fornari et al., 2012)
miR-522	colon cancer	increased expression of ABCB5	(Yang et al., 2015)
miR-92b	colon cancer	reduced expression of SLC15A and SLC15A1	(Dalmasso et al., 2011)
miR-939	gastric cancer	increased expression of SLC34A2; activation of Ras/MEK/ERK pathway	(Zhang et al., 2017)
miR-96	colorectal cancer	reduced expression of anti-apoptotic proteins XIAP and UBE2N	(Kim et al., 2015)
svRNAb	all GI tumours	reduced expression of CYP3A4	(Persson et al., 2009)
vRNA hvg-1	all GI tumours	transporting drugs away from the target and drug sequestration	(Mossink et al., 2003;Gopinath et al., 2010)
vRNA hvg-2	all GI tumours	transporting drugs away from the target and drug sequestration	(Mossink et al., 2003;Gopinath et al., 2010)

885 **Table 2: Overview about the different categories of non-coding RNA molecules**.

886

Name	Biological role
circular RNA (circRNA)	involved in forming RNA-protein complex that regulate gene transcription; involved in regulating gene expression at post-transcriptional level by acting as miRNA sponge
endogenous small interfering RNA (endo-siRNA)	involved in repression of transposable elements, chromatin organisation as well as gene regulation at transcriptional and post-transcriptional level
extracellular RNA (exRNA)	involved in intercellular communication and cell regulation
long intergenic non-coding RNA (lincRNA)	involved in gene expression *via* directing chromatin-modification complexes to specific target regions; lincRNAs located in the cytoplasm function as scaffold to bring together proteins and other RNA categories (especially mRNAs and miRNAs)
long non-coding RNA (lncRNA)	involved in regulation of gene expression *via* binding to chromatin regulatory proteins; involved in regulating gene expression at post-transcriptional level by acting as microRNA decoys; some lncRNAs are processed into microRNAs
microRNA	involved in fine tuning cell homeostasis by controlling gene expression at post-transcriptional level
miRNA-offset-RNA (moRNA)	unknown
piwi-interacting RNA (piRNA)	involved in maintain germline integrity by repressing transposable elements; involved in mRNA de-adenylation;
ribosomal RNA (rRNA)	component of the ribosomes; involved in protein synthesis
small Cajal body RNA (scaRNA)	component of the Cajal bodies; involved in the biogenesis of small nuclear ribonucleoproteins and by this influence splicing of pre-mRNAs
small interfering RNA (siRNA)	involved in RNA interference pathway as part of anti-viral defence
small nuclear RNA (snRNA)	component of the spliceosome; involved in splicing of pre-mRNAs during post-transcriptional modifications
small nucleolar RNA (snoRNA)	component of the Cajal bodies; involved in modification and processing of snRNA, rRNA and tRNA precursors as well as in mRNA editing
sno-derived RNA (sdRNA)	component of the Cajal bodies; involved in alternative splicing of mRNAs; some sdRNAs control gene expression at post-transcriptional level
transcription initiation RNA (tiRNA)	involved in regulation of RNA polymerase II dependent transcription
transfer RNA (tRNA)	involved in transporting amino acids to the ribosomes during translation
vault RNA (vRNA)	component of the vaults (large ribonucleoprotein complexes in

	cytoplasm); unknown function

Table 3: Approved targeted therapies for GI cancer

Abbreviation used: HER2=human epidermal growth factor receptor 2 ; VEGFR=vascular endothelial growth factor receptor; PD-1=programmed cell death protein-1 ; RAF=rapidly accelerated fibrosarcoma; PDGFR=platelet-derived growth factor receptor; c-KIT=SCFR=mast/stem cell growth factor receptor; EGFR=epidermal growth factor receptor; VEGF=vascular endothelial growth factor; RET=rearranged during transfection; MSI-H=microsatellite instability-high

GI cancer	Drug	Target
Gastric cancer	Trastuzumab	HER2
	Ramucirumab	VEGFR-2
	Pembrolizumab	PD-1
Hepatocellular cancer	Sorafenib	RAF, VEGFR-2, VEGFR-3, PDGFR, c-KIT
Colon cancer	Cetuximab, Panitumumab	EGFR
	Bevacizumab	VEGF
	Regorafenib	VEGFR-1, VEGFR-2, VEGFR-3, BRAF, c-KIT, RET, PDGFR
Colon cancer with MSI-H	Pembrolizumab	PD-1

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Figure 1.TIF

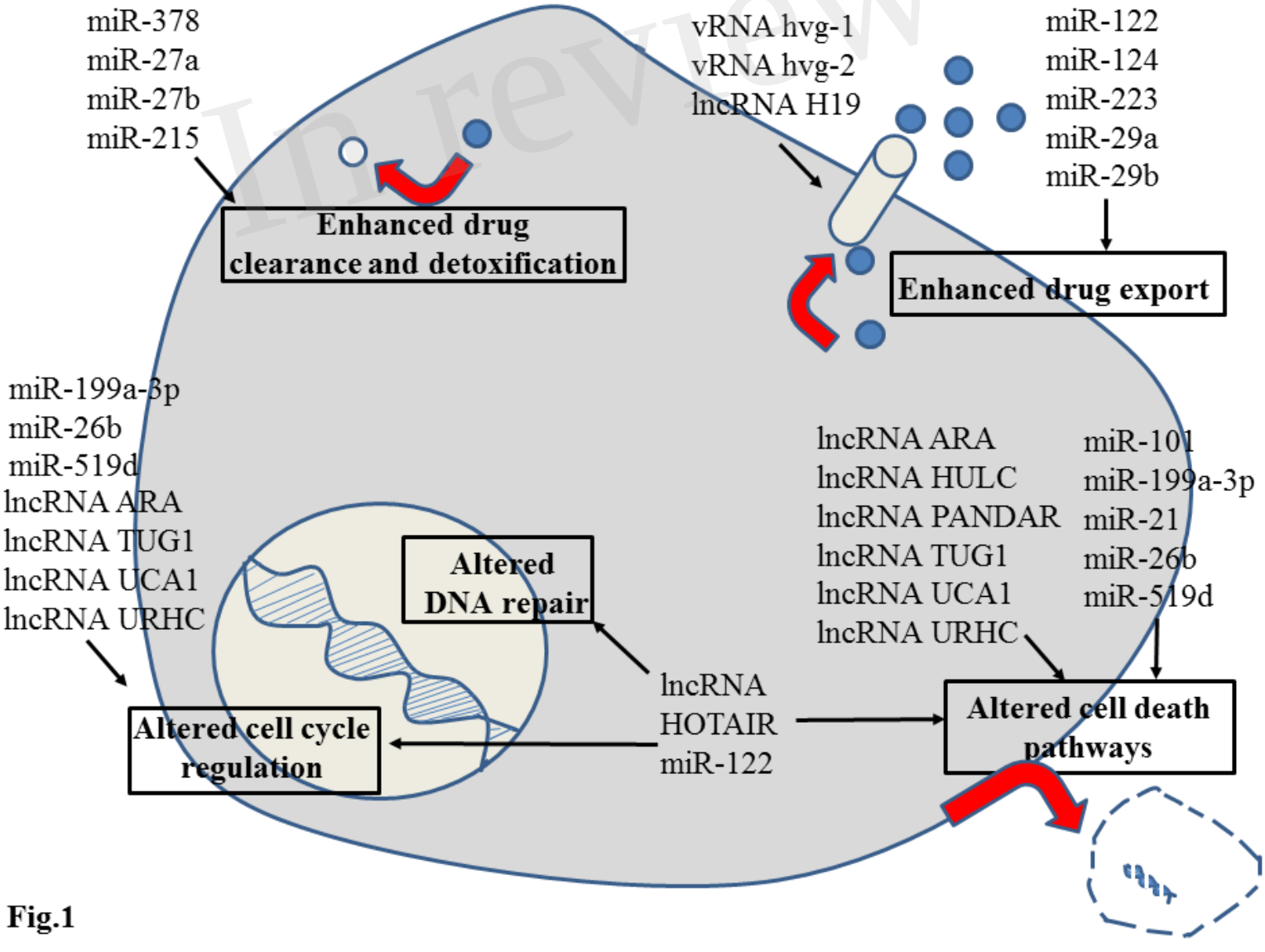

Fig.1

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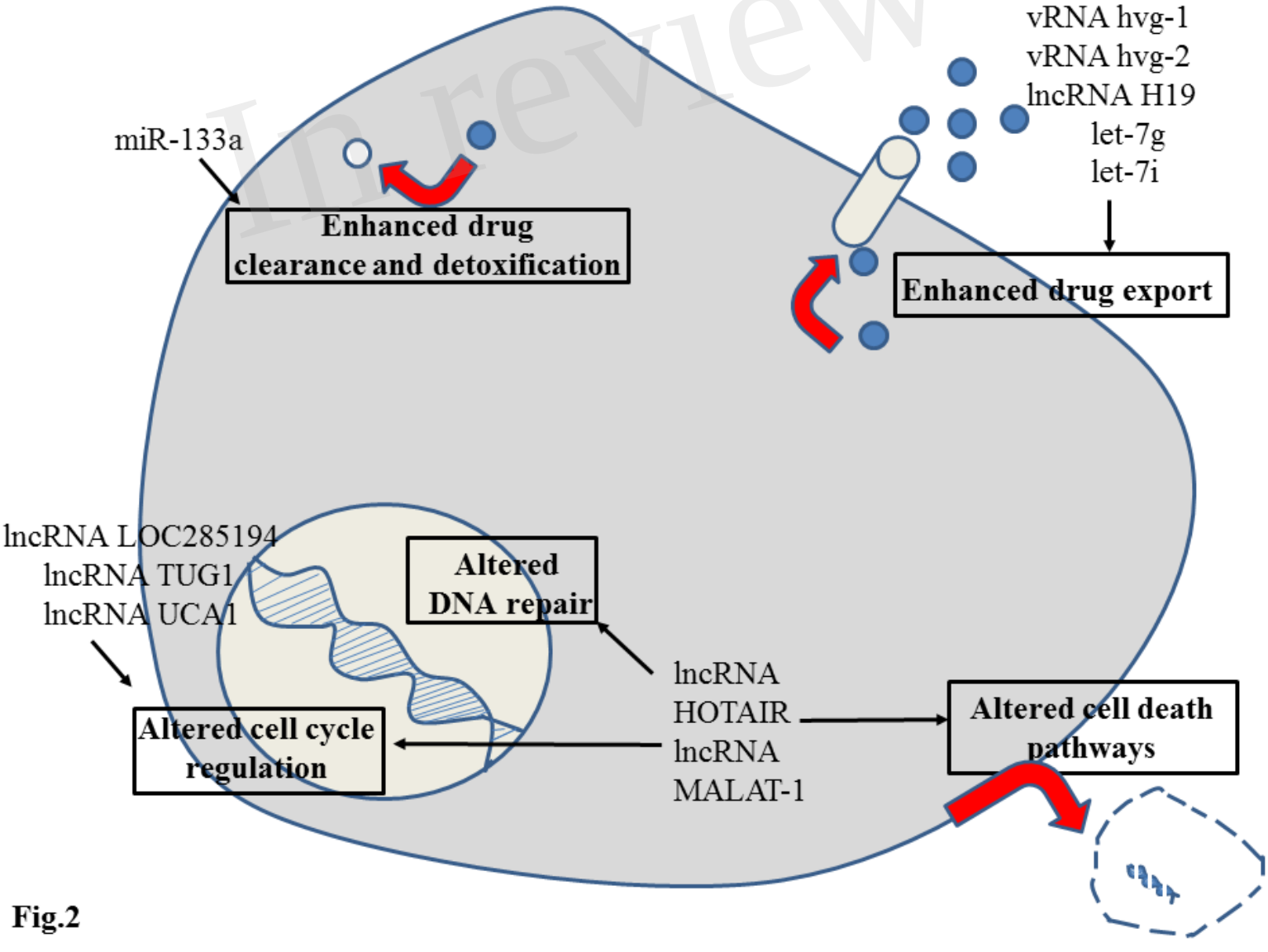

Fig.2

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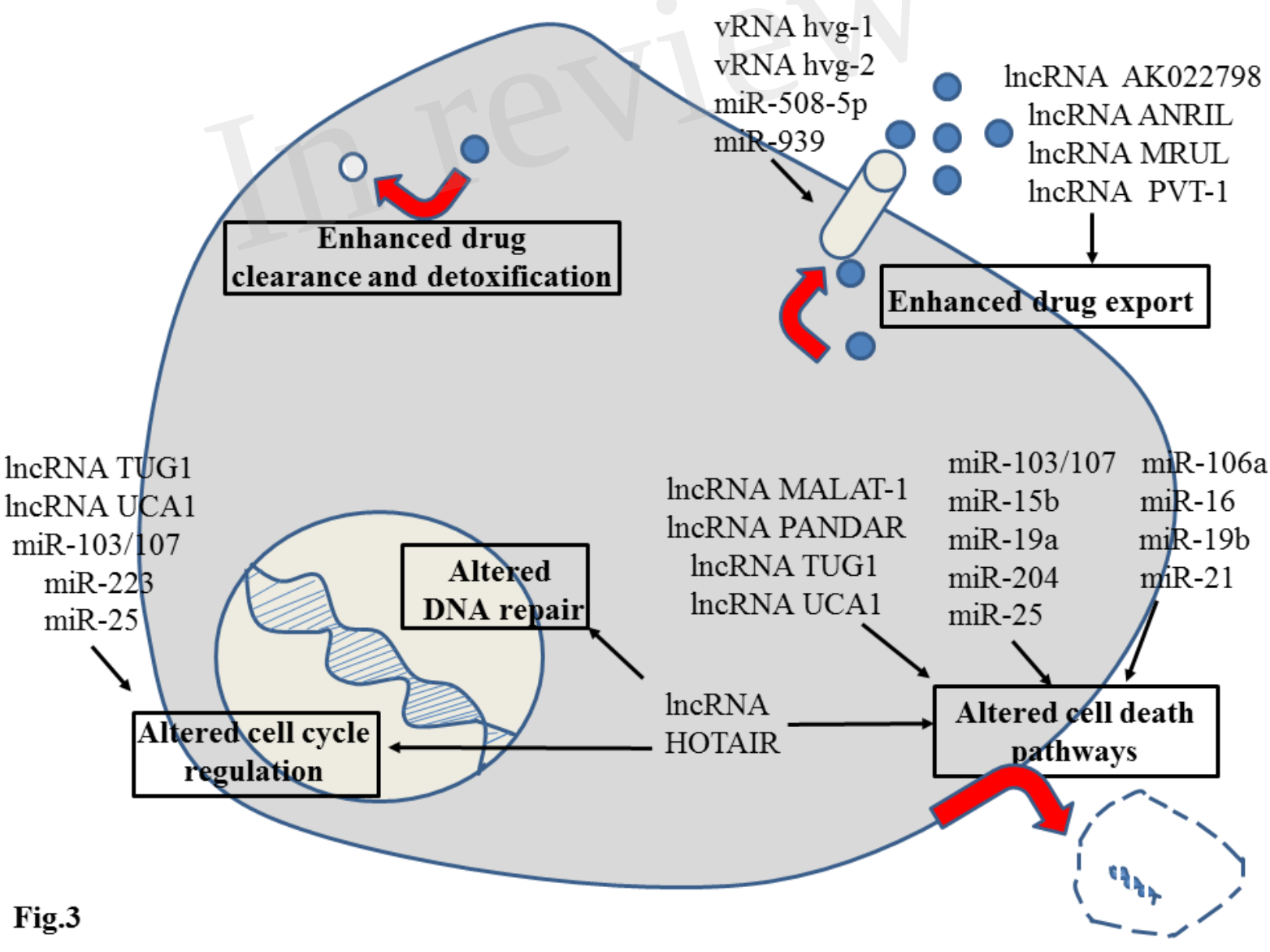

Fig.3

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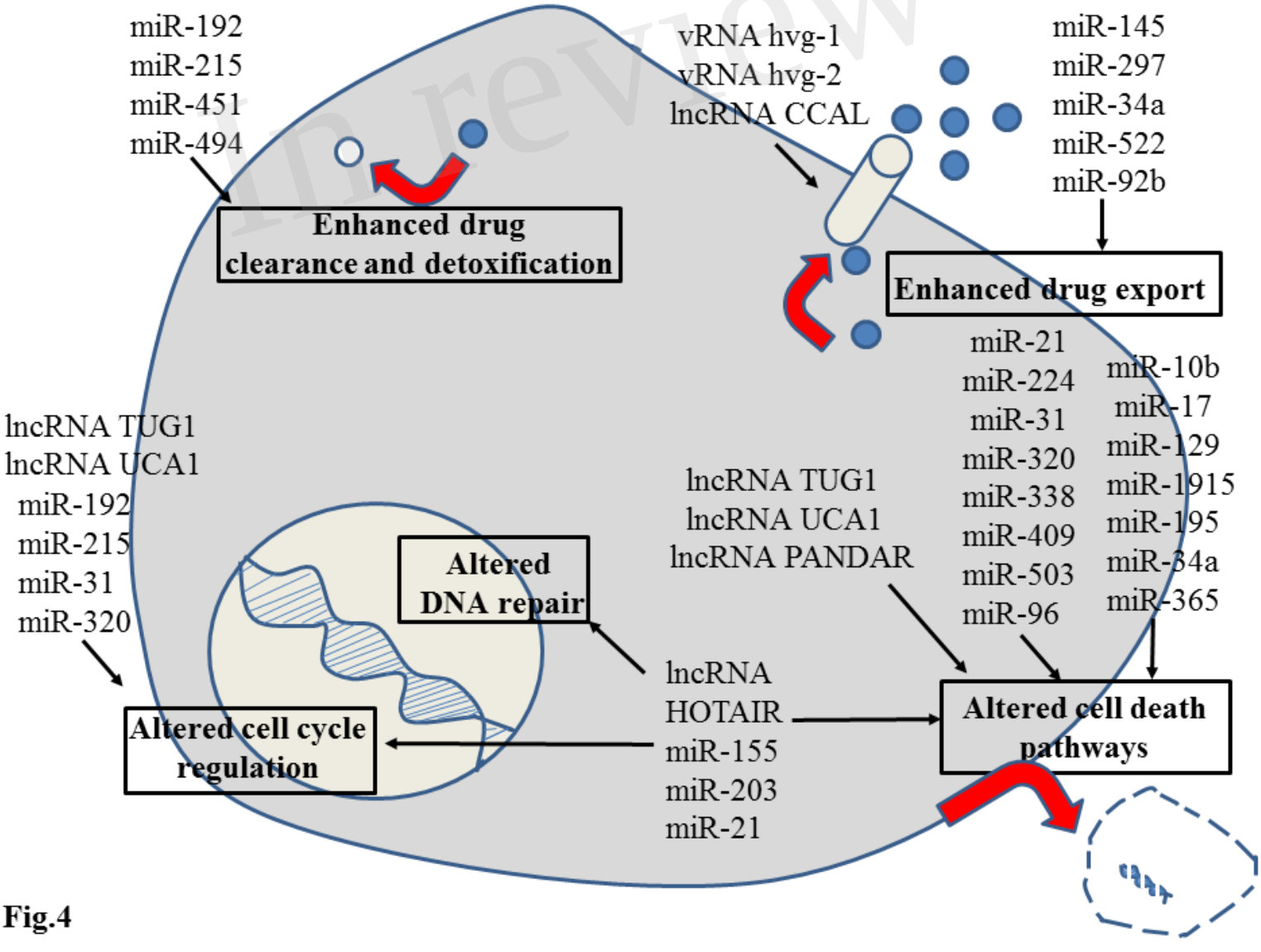

Fig.4

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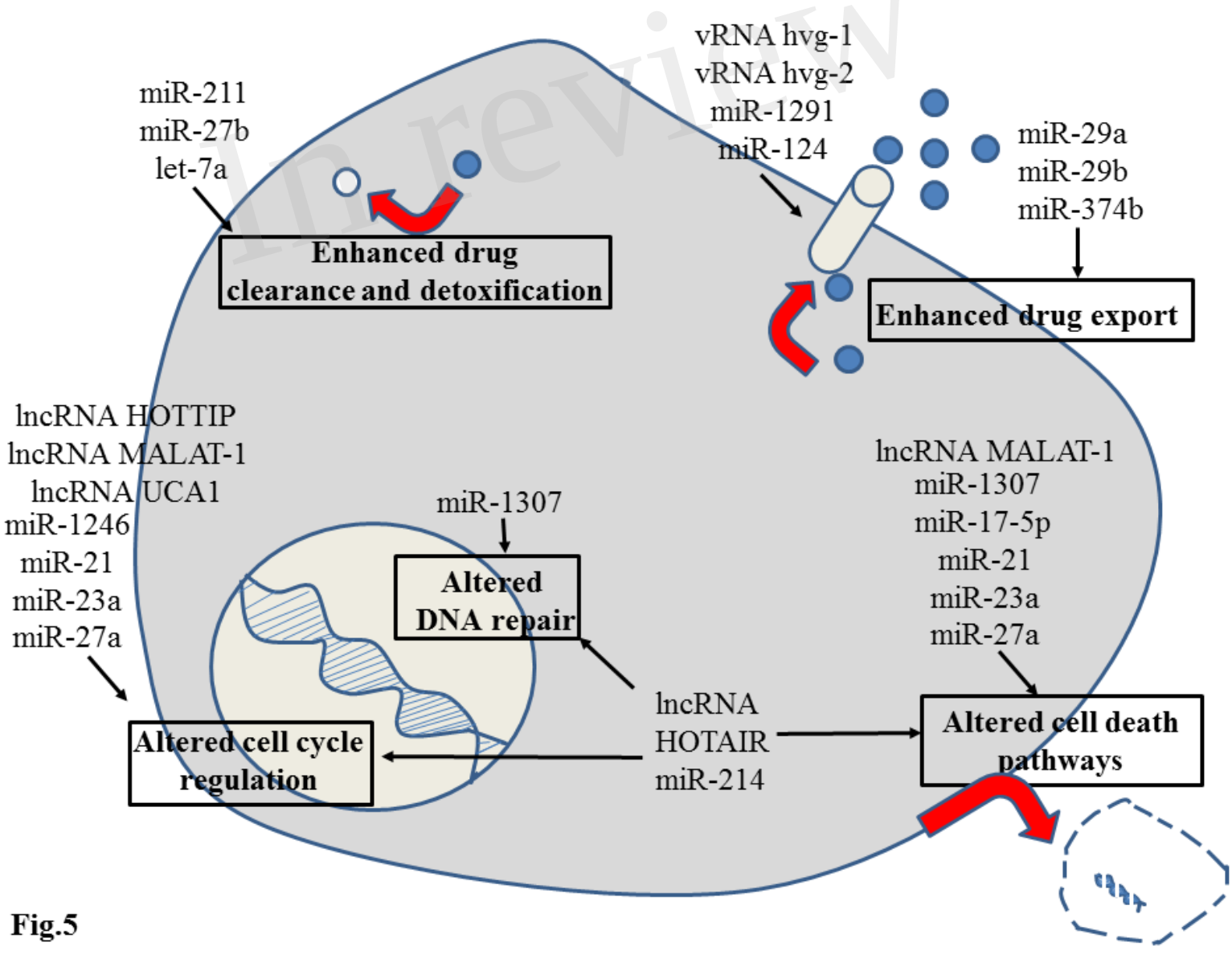

Fig.5

Figure 6.TIF

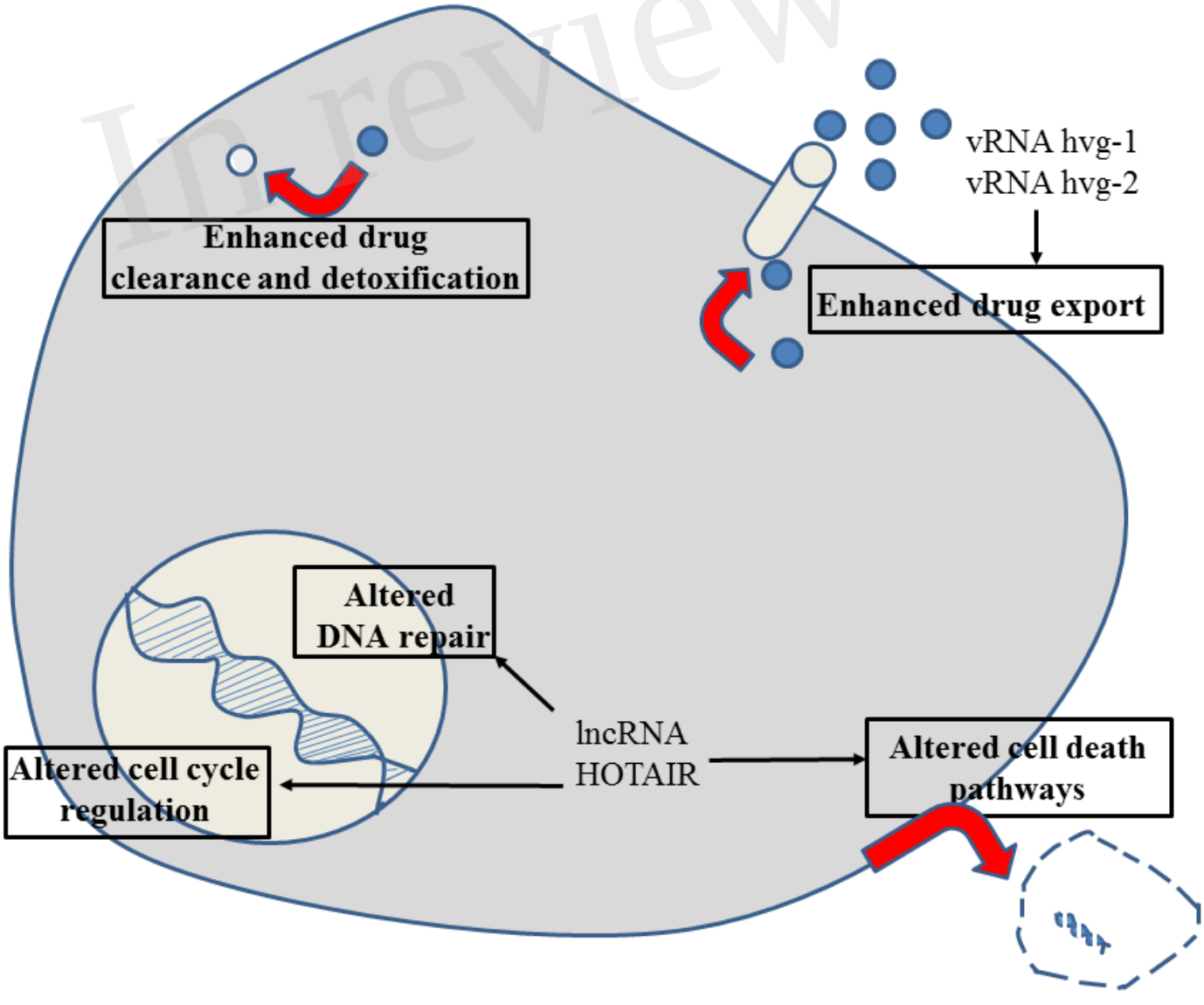

Fig.6

Figure 7.TIF

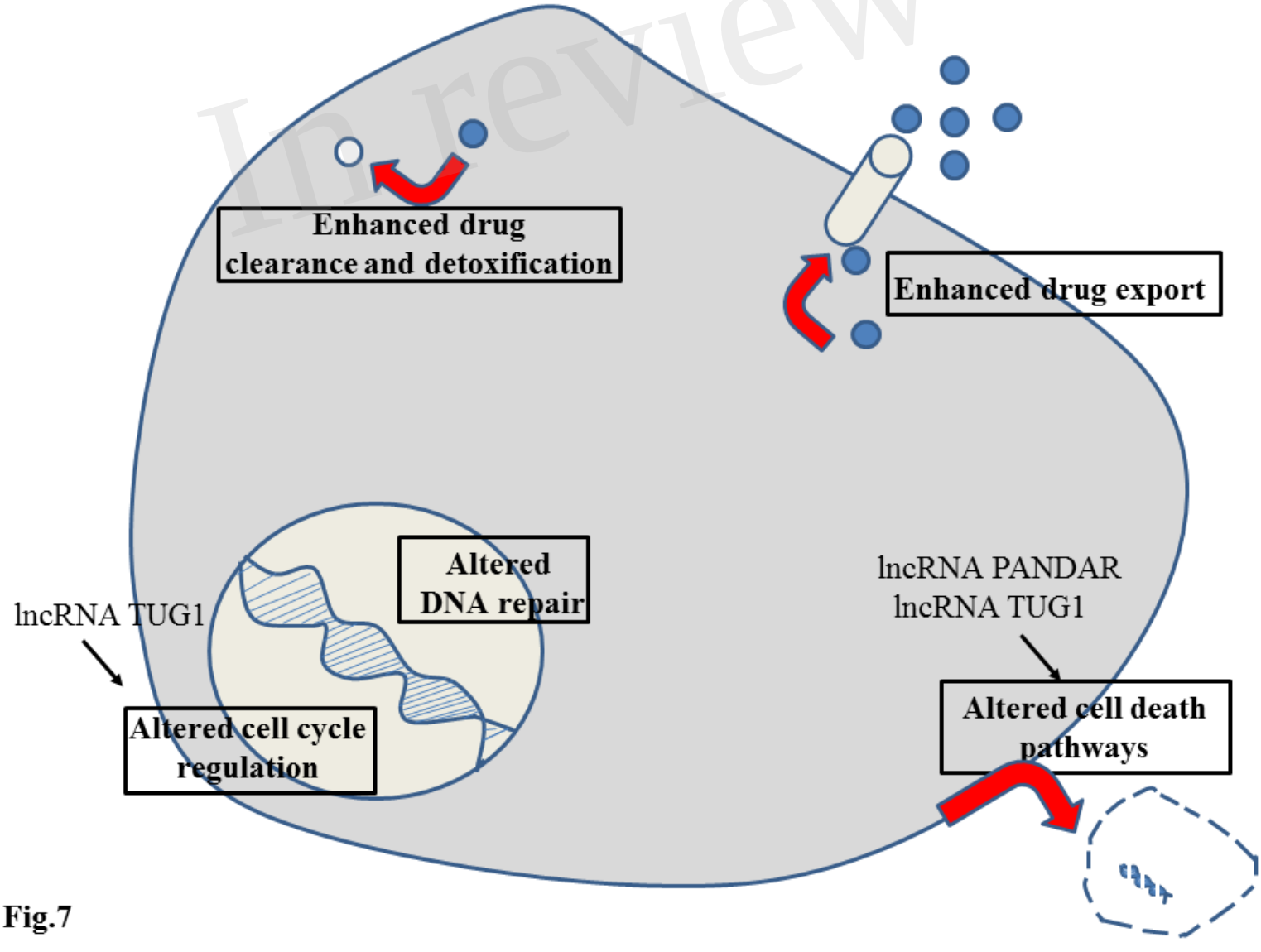

Fig.7