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1 **The influence of long non-coding RNAs**
2 **on the response to chemotherapy in ovarian cancer**

3
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22
23

24 **Abstract**

25

26 With 240,000 new cases and 152 000 deaths per year, ovarian cancer is the leading cause
27 of death from gynecologic malignancies. Late diagnosis because of asymptomatic
28 development in early stages and resistance to existing treatments are the major causes of
29 therapeutic failure in ovarian cancer. The recent discovery of tens of thousands of long non-
30 coding RNAs and their action as oncogenes or tumor suppressors in pathways matching all
31 the hallmarks of cancer in most – if not all – malignancies have attracted attention of the
32 scientific community. A growing number of studies have implicated lncRNAs in diverse
33 aspects of ovarian carcinoma biology. We present lncRNAs which have been involved in
34 response to the different drugs currently used for the treatment of ovarian cancers, from first-
35 line platinum salts and taxanes to the newly available PARP inhibitors. The data already
36 available supports the potential use of several lncRNAs, alone or in combination with other
37 molecules, as potential biomarkers for the prediction of response to treatment.
38 Understanding the determinants of their action might reveal new potential therapeutic
39 targets.

40 **Introduction**

41

42 Ovarian cancer (OC) is the leading cause of death from gynecologic malignancies. It
43 represents around 240,000 new cases and 152,000 deaths per year worldwide[1]. The
44 majority of patients are diagnosed in advanced stages (75% in stage III/IV FIGO). The 5
45 years overall survival is less than 40% for advanced stages[1]. The standard treatment for
46 advanced epithelial OCs consists of a debulking surgery followed by an adjuvant reference
47 treatment combining platinum agents and paclitaxel for 6 cycles +/- bevacizumab. Since
48 residual disease after surgery constitutes the strongest prognosis factor available[2], when
49 complete resection does not seem likely to be readily achievable, a neoadjuvant treatment
50 comprising 3 to 4 cycles of carboplatin and paclitaxel is applied before surgery, in order to
51 increase the likeliness of complete surgical resection. In that scenario another 3 to 4 cycles
52 of carboplatin and paclitaxel +/- bevacizumab are given post-surgery.

53

54 Despite a good response of around 75% of patients to this usual first-line combination
55 therapy, recurrence occurs in most cases together with resistance to treatment[3], which is
56 the major cause of therapeutic failure. Second or third line therapy combines carboplatin and
57 another drug such as paclitaxel, liposomal doxorubicin or gemcitabine, or platinum-free
58 monochemotherapy depending on patient's characteristics[3].

59

60 In recent years, new approaches and numerous clinical trials have been implemented to
61 improve patient's care. However, the implementation of targeted therapies in the treatment of
62 ovarian cancer has lagged behind when compared with other malignancies.

63 However, the anti-angiogenic Bevacizumab[3] has received approval in the United States
64 from the FDA "Food and Drug Administration" and in the European Union from the EMA
65 "European Medicines Agency" as a first-line treatment for the advanced stages (III B, III C
66 and IV) in combination with carboplatin and paclitaxel, or as a maintenance treatment

67 (clinical trials: ICON7, GOG0218)[4]. A moderate improvement in progression-free survival
68 (PFS) was observed, but no long term overall survival (OS) gains have been achieved with
69 anti-angiogenic molecules in OC.

70 More recently, several PARP inhibitors (PARPi) have been approved by EMA and/or FDA for
71 the treatment of OC. The firstly approved molecule was Olaparib in 2014 as a maintenance
72 treatment for 'platinum-sensitive' patients bearing BRCA1/2 mutations[5] followed by
73 Rucaparib and Niraparib for patients who are sensitive to platinum-based chemotherapy,
74 irrespective of BRCA1/2 status[5]. These newly approved treatment options have shown
75 impressive improvements on the PFS[5], and while the results regarding OS are not yet
76 available they hold great promise for the improvement of therapeutic care of OC.

77

78 A better understanding of the mechanisms involved in the response or resistance to
79 treatment is necessary for the development of new therapeutic strategies to predict and/or
80 counter resistance. Resistance of ovarian tumors to various chemotherapeutic agents is a
81 multifactorial process, including but not limited to: increased drug efflux, tolerance to
82 oxidative stress, alterations of DNA repair mechanisms or resistance to apoptosis. Both
83 genetic and epigenetic alterations have been implicated in the alteration of biological
84 pathways related to resistance mechanisms[2].

85

86 The recent advances of high-throughput transcriptomic studies have led to the identification
87 of tens of thousands of non-protein coding RNA transcripts[6] and these non-coding RNAs
88 (ncRNAs) have been demonstrated to regulate gene expression through many
89 mechanisms[6]. Among these ncRNAs, the long non-coding RNA (lncRNA) are defined by
90 the absence of an open reading frame (ORF) and a length above 200 nucleotides[6].

91

92 lncRNAs exert their functions through various mechanisms[7] (**Figure 1**). They can bind
93 RNA and DNA by sequence complementarity, or proteins via their secondary structures. In
94 the cytoplasmic compartment, lncRNAs mainly bind to mRNAs or miRNAs. Binding to

95 mRNAs by sequence complementarity the 5'UTR can upregulate translation, whereas 3'UTR
96 complementarity with ALU repeats destabilizes mRNAs and decreases expression levels of
97 the corresponding protein[7]. Another mode of action is the widely described binding to
98 miRNAs by sequence complementarity with their seed regions, efficiently sequestering
99 miRNAs away from their mRNA targets, thereby derepressing their expression. LncRNAs
100 sequestering miRNAs have been termed "Competing Endogenous RNAs (ceRNAs).
101 Interestingly, some lncRNAs can also act as precursors of miRNAs[8].

102 In the nucleus, lncRNAs functions rely on three main modes of action, as guides, decoys or
103 scaffolds. Guide lncRNAs address protein complexes such as Trithorax (MLL) or Polycomb
104 (PRC1, PRC2) to specific loci in the genome, where they deposit histone post-translational
105 modifications to epigenetically enhance or inhibit gene expression[8]. Decoy lncRNAs
106 associate with proteins such as transcription factors, and prevent them to act on their target
107 sequences in the genome[7]. Scaffold lncRNAs also associate with proteins complexes
108 through their secondary structures, thus enabling assembly of larger complexes and allowing
109 the coordinated action of several complexes in the same loci in the genome.

110 It is important to note that these multiple modes of action are not mutually exclusive, and a
111 single lncRNAs can act through several different mechanisms. For example, H19 act as a
112 scaffold for PRC2 complex, as a ceRNA by sponging miR-29a[9], and as a precursor of miR-
113 675[10].

114 lncRNAs regulate many biological processes such as imprinting, differentiation,
115 development or cell cycle[8]. They also have functions in many cancers, if not all, where they
116 can act as oncogenes or tumor suppressors[11]. Several studies have demonstrated the
117 essential roles of several lncRNAs such as PVT1, HOTAIR, UCA1 or MEG3 in the resistance
118 of various tumors to chemotherapeutic agents[12] including in OC.

119
120 The objective of this review is to present the lncRNAs involved in resistance or response to
121 the chemotherapeutic agents and targeted therapies used in the treatment of OC. The study
122 of lncRNAs could help to better understand the determinants of the response to these

123 treatments, should help to define new, tools useable for the prognosis and/ or predictive of
124 the response to treatment, and might lead to the proposal of new innovative therapies.

125

126 **LncRNAs involved in the response to first-line chemotherapy**

127

128 The deregulation of numerous lncRNAs in OC and their involvement in mechanisms
129 modulating the response of OC cells to the action of taxanes and platinum salts has now
130 been acknowledged in many studies[13,14].

131

132 Initially cisplatin (cis-diamine dichloroplatinum(II)) was the first platinum compound to be
133 used in the treatment of OC[13]. Carboplatin (cis-diamine cyclobutane-1,1-dicarboxylate-O,O'
134 platinum(II)) is the second platinum complex used in OC treatment. It is known to have the
135 same ability to form DNA adducts as cisplatin, but with lower side effects, less toxicity and a
136 slower reactivity[15]. Paclitaxel (Taxol) is used in OC first-line therapy and exerts its action
137 through preventing microtubules de-polymerization and therefore blocking cancer cells in the
138 G2/M phase [16].

139

140 Out of the several lncRNAs which have been associated with the response to first line
141 treatment in ovarian cancer cells, we chose to present only the ones for which data regarding
142 their mechanisms of action have been made available.

143

144 **UCA1** (Urothelial carcinoma-associated 1) is located on human chromosome 19p13.12, is
145 composed of three exons and two introns and presents three isoforms. These isoforms are
146 different by their sizes: 1.4Kb, 2.2Kb and 2.7Kb. The 1.4Kb isoform is the most studied
147 isoform and is involved in the development of several cancers[17]. UCA1 is an oncofetal
148 lncRNA expressed mainly in embryonic tissues, and physiologically only at apparently low
149 levels in cardiac tissue in adults[18]. It has been proven that UCA1 is re-expressed and has

150 an oncogenic role in hepatocellular carcinoma, gastric, bladder, breast, colorectal and OC.
151 UCA1 is able to promote proliferation, metastasis, and invasion[19]. Moreover, UCA1 has
152 been shown to contribute to the development of resistance to many chemotherapeutic
153 treatments including cisplatin or paclitaxel in OC[17,20].

154 It has been demonstrated that UCA1 expression is upregulated in OC and this
155 overexpression promotes cell migration, invasion and cisplatin resistance[21]. UCA1
156 promotes upregulation of SRPK1 (Serine/threonine-protein kinase 1) and Bcl-2 (an anti-
157 apoptotic protein) expression and decreases expression of many pro-apoptotic factors such
158 as Bax, Caspase 3 and Caspase 9. SRPK1 belongs to the SR kinase family and is able to
159 regulate gene expression by acting on pre-mRNA splicing. It has been previously shown that
160 SRPK1 increases cisplatin resistance in OC[22].

161 It has been also described that UCA1 is overexpressed in paclitaxel-resistant OC cells and
162 promotes the acquisition of resistance to this agent by its role of ceRNA on miR-129,
163 therefore upregulating ABCB1 protein, a direct target of miR-129[20]. MiR-129 is known to be
164 involved in drug sensitivity in many cancers such as breast cancer[23]. ABCB1/Pglycoprotein
165 (P-gp) is an efflux pump and plays a role in the elimination of chemotherapeutic agents and
166 therefore participates in resistance mechanisms in OC cells[24].

167 In oral squamous cell carcinoma, UCA1 is also involved in the resistance to cisplatin, through
168 sponging miR-184[25]. Interestingly, it has been shown that high miR-184 levels in OC cells
169 represses proliferation and induces apoptosis, suggesting a possible induction of
170 chemoresistance by sponging miR-184[26].

171

172 **HOTAIR** (HOX Transcript Antisense RNA) is one of the most studied lncRNAs. It is an
173 antisense RNA transcribed from the mammalian HOXC gene cluster[27]. This oncogenic
174 lncRNA is involved in many cancers such as gastric, colorectal, breast or OCs[27], mainly
175 through its guide and scaffolding functions. HOTAIR has been shown to be involved in the
176 development of resistance to various chemotherapeutic agents such as cisplatin.

177 It was demonstrated that the overexpression of HOTAIR promotes cisplatin resistance in OC
178 by the activation of Wnt/ β -catenin pathway[27]. HOTAIR is able to modulate the expression
179 of cyclin D1, its ligand CDK4 and β -catenin, thus activating the Wnt/ β -catenin signaling
180 pathway, which is often deregulated in OC[28].

181 HOTAIR was identified as playing a role in cisplatin chemoresistance in gastric cancer by
182 activation of PI3K/AKT/MRP1 pathway *via* its inhibiting role on miR-126[29], which could be
183 relevant in OC because of the prominent role of PI3K/AKT pathways in chemoresistance of
184 OC cells.

185 In lung adenocarcinoma HOTAIR downregulates p21 and therefore promotes resistance to
186 cisplatin[30]. A similar mechanism could promote OC chemoresistance as well, since p21
187 downregulation triggers resistance to cisplatin in OC cells[31].

188

189 **PVT1** (plasmacytoma variant translocation 1) is a long non-coding RNA located on
190 chromosome 8q24 near the MYC locus[32]. It is known to have an oncogenic role with
191 involvement in various pathways that promote tumor growth, proliferation, invasion, and
192 metastasis, and also represses apoptosis in various cancers[33].

193 PVT1 is also known for its involvement in the resistance to cisplatin in OC, and it has been
194 described as a regulator of the apoptotic pathway of OC cells leading to cisplatin
195 chemoresistance[32]. The expression of PVT1 is increased in tumor tissues of cisplatin-
196 resistant patients and in OC cells and its inhibition allowed sensitizing to cisplatin action,
197 most likely through the upregulation of Caspase 3 expression. The mechanisms of action by
198 which PVT1 mediates its effects remain to be elucidated.

199 PVT1 has also been identified as being involved in the response of OC cells to treatment
200 combining carboplatin and docetaxel[34]. In this study PVT1 has been described as a tumor
201 suppressor, promoting the anticancer action of these chemotherapeutic agents by an
202 upregulation of P53 and TIMP1 expression. P53 is the best known tumor suppressor, but it is
203 inactivated in more than 95% of high-grade serous OCs, thus the action of PVT1 through
204 P53 is most likely minor in OC. TIMP1 (TIMP Metallopeptidase Inhibitor 1) is an inhibitor of

205 matrix metalloproteinase, and has therefore tumor suppressor activities in many cancers
206 including ovarian[35].

207 Whether PVT1 in OC is acting as an oncogene or tumor suppressor is most likely context
208 dependent and further studies will be needed for a better understanding of its functions.

209

210 **XIST** (X-inactive specific transcript) originates from the XIST gene on X chromosome and is
211 a major player of the X inactivation in women by interaction with PRC2. XIST expression is
212 present in all normal female cells but can be decreased or absent in female cancer cell lines,
213 such as breast, cervical and OCs[8]. XIST functions in cancer depends on the context: it is
214 known to act as a tumor suppressor in OC with an inhibitory role on many tumor processes
215 such as proliferation, invasion and resistance to cisplatin[36], whereas XIST acts as an
216 oncogene in non-small cell lung cancer[37].

217 It has been shown in epithelial OC (EOC) cells (CAOV3/OVCAR3) that XIST is lowly
218 expressed and that the upregulation of its expression promotes anticancer effects through its
219 sponging of miR-214-3p by direct interaction with this miRNA[36]. XIST then competes with
220 mir-214-3p and prevent it to act on its targets, such as PTEN, and therefore prevents this
221 miRNA to exert induce cisplatin resistance in EOC[38].

222

223 **H19** is an imprinted oncofetal gene located on the human chromosome 11p15.5, which is
224 known to play an essential role in embryonic development and cancer progression. It is
225 deregulated in many cancers such as bladder, breast, colorectal, esophageal and OCs[8].
226 This lncRNA acts as an oncogene by promoting tumor development, metastasis, epithelial-
227 mesenchymal transition, or by allowing the acquisition of chemoresistance to multiple
228 chemotherapeutic drugs including cisplatin in OC.

229 It has been demonstrated that in OC cells H19 expression was triggered after cisplatin
230 treatment in sensitive cells and upregulated in cisplatin-resistant cells and its inhibition
231 promotes sensitivity to cisplatin. H19 is thought to act by regulating glutathione (GSH)

232 metabolism and NRF2 targets[39]. NRF2 belongs to the GSH pathway and is a regulator of
233 various antioxidant molecules, a pathway involved in cisplatin resistance in OC[40].

234

235 **BC200** (Brain cytoplasmic 200) is involved in carboplatin resistance of OC. BC200 is a small
236 cytoplasmic non-messenger RNA of about 200 nucleotides. This lncRNA is physiologically
237 expressed in the human nervous system. It has been demonstrated that BC200 expression
238 is associated with cancer cells from malignancies originating from various tissues such as
239 breast, esophagus, lungs, cervix and ovaries.

240 It has been shown that the expression of BC200 is decreased in OC cells compared to
241 normal cells, promoting cell proliferation and carboplatin resistance[41]. In addition,
242 carboplatin-induced BC200 expression promotes the sensitivity of cancer cells, highlighting a
243 tumor suppressor role for BC 200. The mechanism through which BC200 is induced or
244 operates remains to be elucidated.

245

246 **NEAT1** (Nuclear paraspeckle assembly transcript 1), is located on human chromosome
247 11[42]. This lncRNA is a component of the paraspeckles, a nuclear structure whose functions
248 are only poorly defined. NEAT1 is known for its oncogenic role in many cancers, including
249 OC, where it promotes cell proliferation, migration and apoptosis[43].

250 It has been demonstrated that NEAT1 is increased in paclitaxel-resistant OC cells and
251 tissues and an increase of its expression is involved in the acquisition of resistance. It is
252 explained by its ability to induce ZEB1 (zinc finger E-box-binding homeobox 1) expression
253 through sponging miR-194[42]. It has been also demonstrated that ZEB1 plays an important
254 role in many cancers' progression including OC, and that ZEB1 is involved in the resistance
255 to many drugs such as doxorubicin, gemcitabine and paclitaxel[44].

256

257 **FER1L4** (Fer-1-like protein 4) is downregulated in various cancers and a role of FER1L4 in
258 paclitaxel tolerance in OC cells was demonstrated[45]. Low expression of FER1L4 allows
259 tumor growth and the development of chemoresistance by the regulation of MAPK signaling

260 pathway, implicated in cisplatin chemoresistance of OC[46], although the mechanisms of
261 FER1L4 action are not precisely described.

262

263 **LncRNAs involved in angiogenesis and possibly in response to** 264 **Bevacizumab**

265

266 The biological process of angiogenesis is one of the pivotal hallmarks of cancer where it
267 induces tumor development through the formation of new vessels. This neovascularization
268 will depend on a balance between pro- and anti-angiogenic factors. The key angiogenic
269 growth factors are vascular endothelial growth factor (VEGF), platelet derivative growth
270 factor (PDGF) and fibroblast growth factor (FGF), and their receptors. These are positively
271 regulated in tumors, thus promoting their growth, hence the relevance of the design of
272 targeted therapeutics to counteract tumor neo-angiogenesis. The anti-angiogenic agent
273 currently used in the treatment of OC is bevacizumab. It is a recombinant humanized
274 monoclonal antibody that binds to VEGF and prevents it to promote tumoral neo-
275 angiogenesis[3,4].

276

277 To date, no study to our knowledge has demonstrated the involvement of lncRNAs in
278 regulating the response of cancer cells to anti-angiogenic action. To our knowledge, only one
279 study has demonstrated a direct link between a lncRNA and angiogenesis in OC, while only
280 a few other studies have reported such a connection in other malignancies such as bladder,
281 breast, liver cancers and glioblastoma[47,48].

282

283 **MALAT1** has been identified as being transferred by (EOC) cells to HUVECS (human
284 umbilical vein endothelial cells) *via* exosomes. This transfer not only stimulates tumor growth
285 but also the expression of pro-angiogenic genes such as VEGF and FGF, and increases
286 angiogenesis in tumors *in vivo* in nude mice[48].

287

288 **H19** has been shown to be overexpressed in microvessels and their associated endothelial
289 cells in a glioma model, where it sponges miR-29a, a miRNA able to directly target
290 vasohibin2 (VASH2). Therefore, VASH2 is upregulated, promoting angiogenesis in glioma
291 [9]. This mode of action could add to the previously described deleterious effects of H19
292 regarding the response to cisplatin in OC cells. Moreover, independently of its role in
293 angiogenesis, down regulation of miR-29a has also been shown to promote cisplatin
294 resistance in OC cells[49].

295

296 **LncRNAs involved in DNA repair and possibly in response to PARPi**

297

298 The study of DNA damage response and manipulation of this process is now recognized as
299 an important area of research and could lead to an improvement of OC therapeutic care.
300 PARP (Poly-ADP ribose polymerase) has an important role in the repair of single-strand DNA
301 breaks (SSB) and the use of PARP inhibitors (PARPi) can result in double-strand breaks
302 (DSB). DSB normally would be repaired by Homologous Recombination (HR) DNA repair
303 pathway which is a complex process involving many proteins, notably BRCA1 and BRCA2.
304 In HR-deficient (HRD) tumors, alternative DNA repair by non-homologous end joining
305 (NEHJ), a low fidelity repair mechanism, eventually results in cell death[50].

306

307 PARPi have been identified as a particularly beneficial treatment for patients bearing
308 *g/sBRCAmt*, however they represent only a small portion of high-grade serous OC cases
309 (HGSOC)[51]. Importantly, patients with *g/sBRCAmt* achieved longer progression-free
310 survival (PFS), although results among patients without *g/sBRCAmt* treated by PARPi were
311 better than those with placebo. These evidences suggest that patients with other defects
312 (regardless of BRCA status) in the HR DNA repair system (HRD patients), such as

313 alterations in ATM, CHEK2, PALB2, RAD51C, RAD51D, etc., may also benefit from
314 PARPi[52].

315 Germline and somatic mutations in HR genes are present in approximately one-third of OCs
316 and also predict a better response to primary platinum-chemotherapy. More broadly, the
317 HRD status reflects all alterations leading to HR abnormalities and conferring sensitivity to
318 platinum and PARPi. To date, the HRD status has been partially determined through the
319 analysis of gene mutations *via* multigene panel testing or through different HRD assays,
320 some of them studying genomic instability. However, the determinants of response to PARPi
321 remain incompletely characterized, and important efforts are made to identify molecular
322 signatures as well as functional assays able to predict the response to PARPi.

323

324 To date, lncRNAs involved in HR or NHEJ have not been documented in OC. However,
325 given the large number of lncRNAs and their diverse functions, it is not surprising that
326 several lncRNAs play intricate roles in genome integrity maintenance and in the DNA
327 damage response, and more particularly in DSB repair[53].

328

329 **PCAT-1** (Prostate Cancer Associated Transcript 1) is overexpressed in prostate cancer,
330 downregulates BRCA2 and impairs HR, which, in turn, sensitize prostate cancer cells to
331 PARP inhibitors[54]. The mechanism by which PCAT-1 down-regulates BRCA2 is at least in
332 part by a post-transcriptional repression of the 3' UTR of BRCA2 mRNA. Interestingly, PCAT-
333 1 levels are inversely correlated with RAD51 foci formation when prostate cancer cells are
334 treated with PARPi. A recent study has shown that this lncRNA, overexpressed in OC cell
335 lines and tumors, could be involved in the development and progression of OC[55]. However,
336 no information was provided regarding the response to platinum-based chemotherapy or
337 innovative treatments such as PARPi.

338

339 **DDSR1** (DNA Damage-Sensitive RNA1) has been proposed to have a role in modulating
340 DNA repair by HR[56]. DDSR1 expression is induced by ATM in immortalized human skin

341 fibroblasts. Moreover, DDSR1-depleted cells present a defective HR and show increased
342 sensitivity to PARPi. The HR defect in the absence of DDSR1 is noticeable by aberrant
343 accumulation of BRCA1 and RAP80 at DSB sites. In agreement with a role in regulating HR,
344 DDSR1 interacts with BRCA1 and hnRNPUL1, an RNA-binding protein involved in DNA end
345 resection, and thus likely acts through a scaffolding mechanism. To our knowledge, this
346 lncRNA has never been studied in OC.

347

348 **NEAT1** levels in cholangiocarcinoma (CCA), are negatively correlated with BAP1 (BRCA-1
349 associated protein-1) according to TCGA dataset. BAP1 is a member of the ubiquitin C-
350 terminal hydrolase superfamily that plays a critical role in chromatin remodeling[57]. The
351 knockdown of BAP1 by upregulating NEAT1 expression sensitizes CCA cells to
352 chemotherapy and PARPi.

353 In a study in an OC model, the authors reported that NEAT1 was a ceRNA for miR-506 to
354 promote cell proliferation and migration[58]. MiR-506 is targeting directly RAD51 mRNA, and
355 its systemic delivery in *nude* mice improved the response to cisplatin and olaparib[59].

356

357 **NORAD** (non-coding RNA activated by DNA damage), is located on chromosome 20q11 and
358 his length is 5.3 kb. NORAD is expressed abundantly, ubiquitously and is necessary to
359 maintain genomic stability[60].

360 It was identified NORAD as being involved in genome stability through the interaction with
361 RBMX, an element of the response to DNA damage. This RNP complex associates with
362 other proteins, including TOP1, a known promoter of genomic stability. NORAD inhibition
363 induces defects in DNA replication and chromosome segregation[60]. It has also been shown
364 that NORAD sequesters PUMILIO proteins, which otherwise repress DNA repair and induces
365 genomic instability. Oncogenic roles of NORAD have been shown in cancer cells from
366 different origins, including ovarian[61].

367

368

369 **LncRNAs involved in response to 2nd and 3rd line treatments**

370

371 Second and third line treatments upon relapse are indicated depending on the patient's
372 response to first-line treatments. For platinum-sensitive patients, therapy combining platinum
373 salt and paclitaxel or liposomal doxorubicin or gemcitabine is indicated. For patients
374 refractory or resistant to platinum, platinum-free monochemotherapy is recommended, with
375 paclitaxel, doxorubicin, topotecan or gemcitabine.

376

377 Doxorubicin (liposomal pegylated doxorubicin; Adriamycin) is a cytotoxic antibiotic belonging
378 to the anthracycline family, whose anti-tumor effects mainly depend on the ability to inhibit
379 the action of topoisomerase II and thus create DNA damage and apoptosis of cancer
380 cells[62].

381 Gemcitabine is a pyrimidine nucleoside antimetabolite analog (20,20-Difluoro 20-
382 deoxycytidine, dFdC) able to replace cytidine during DNA replication and therefore inhibit
383 DNA synthesis and cause apoptosis[62].

384 Topotecan is a topoisomerase I (TOP1) inhibitor which binds to TOP1-DNA cleavage
385 complex. This complex between topotecan-TOP1-DNA interferes with the replication fork and
386 leads to apoptosis of the cells[63].

387

388 To date, no studies have identified in OC the involvement of lncRNAs in the mechanisms
389 regulating the resistance of these drugs, which is not entirely surprising since they play a
390 minor role compared to platinum salts in the treatment of this disease, and they are therefore
391 less often studied in this context. However, in other malignancies, several lncRNAs have
392 been shown to play a role in the response to these drugs. The mechanisms of action which
393 could be relevant in OC are presented below.

394

395 **UCA1** in breast cancer cells promotes doxorubicin chemoresistance through a mechanism
396 involving the heterogeneous nuclear ribonucleoprotein I (hnRNPI) and P27 (Kip1)[64].
397 HnRNPI is located in the cytoplasm after doxorubicin treatment and binds to p27 (Kip1)
398 mRNA, a known tumor suppressor, to promote its translation[65]. It has been demonstrated
399 that hnRNPI is able to bind UCA1 creating a competition between p27 and UCA1. UCA1
400 overexpression therefore leads to a decrease in p27 protein levels.

401

402 **PVT1** has been shown to increase the resistance of osteosarcoma cells to gemcitabine[33]
403 where it is a ceRNA to miR-152, sponging it away from its target c-Met. In OC cells, targeting
404 c-Met has been shown to enhance sensitivity to paclitaxel[66]. Interestingly, c-MET inhibition
405 also prevents PARP1 phosphorylation, thereby enhancing breast cancer cells response to
406 PARP inhibitors. In addition to other roles of PVT1 in chemoresistance of OC cells, this
407 pathway might be of significant value to predict or potentiate OC response to the newly
408 introduced PARP inhibitors[67].

409

410 **TUG1** is upregulated in bladder urothelial carcinoma (BUC) where it is associated with a poor
411 response to doxorubicin chemotherapy[68]. TUG1 influences doxorubicin resistance in this
412 cancer by the regulation of Wnt/ β -catenin pathway, which is known to be involved in
413 tumorigenesis and response to treatment in OC[27]. TUG1 has also been shown to increase
414 ovarian cancer cell proliferation and decrease apoptosis, although the involvement of Wnt/ β -
415 catenin pathway was not assessed in this study[69].

416

417 **H19** is upregulated in doxorubicin resistant breast cancer cells, and plays a leading role in
418 this resistance by increasing the expression of ABCB1/MDR1, a drug efflux factor involved in
419 drug resistance in different context, including OC[70].

420

421

422 **Conclusions and perspectives**

423

424 In summary, the mechanisms by which lncRNAs modulate response to the drugs used for
425 the treatment of OC are diverse and can occur at every step of the action of
426 chemotherapeutic drugs: from drug efflux to diverse pro-survival or anti-apoptotic pathways,
427 including the management of genome stability and the response to DNA damage.

428 While many studies[8], have correlated altered expression of lncRNAs with the prediction of
429 disease-free survival and overall survival in OC, none of these candidate have been turned
430 so far into reliable and clinically useable biomarkers able to predict patient's survival and
431 response to available treatments.

432 The definition of such biomarkers will need an increased number of discovery and validation
433 studies, preferably in cohorts of homogenous subtypes of OC. Since the different histologies
434 and subtypes of OC constitute different diseases at the histological and molecular levels, it is
435 expected that no common biomarker will be defined for the full range of OC subtypes. In this
436 regard, lncRNAs for which a role in the response to treatment has been identified might
437 constitute valuable candidates to refine the predictive value of other biomarkers. For
438 instance, a given lncRNA with a role as ceRNA for a given miRNA might hold a predictive
439 value only in light of the expression level of the miRNA.

440 The growing evidence about lncRNAs suggests that alone or in combination with other
441 factors (protein coding genes, lncRNAs or miRNAs) lncRNAs may serve as biomarkers that
442 are highly valuable and desirable for prognosis and prediction of the response to therapies,
443 including the newly available and highly promising PARP inhibitors in OC.

444 Although the study of lncRNAs is still in its infancy, this is a highly dynamic field of research
445 and accumulation of knowledge about their roles and functions in the biology of OC will
446 eventually lead to the identification of innovative potential therapeutic strategies. RNA
447 interference is quite relevant to target specific lncRNAs but such strategies have failed so far
448 to successfully enter the clinics and their use, while likely to become available in the future,

449 might still remain years ahead. However, a detailed knowledge of the mechanisms of action
450 of lncRNAs, and of the genes whose expression they regulate, could enlighten relevant
451 target which could be druggable through more commonly used drug design strategies.

452 Altogether, the raising *corpus* of knowledge about the roles and functions of lncRNAs in the
453 biology of OC may provide highly relevant tools to predict the response to treatments, as well
454 as seed the definition of innovative therapeutic strategies in the years to come.

455

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457

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466

467 **Conflict of interest**

468

469 The authors declare no conflict of interest

470

471 **Author contribution**

472 **Anaïs Wambecke**: Conceptualization, Writing – Original Draft. **Mohammad Ahmad**: Writing
473 Review & Editing. **Bernard Lambert**: Writing – Original Draft. **Florence Joly**: Writing Review
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476 Conceptualization, Writing – Original Draft.

477

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704

705 **Table legend**

706

707 **Table1:** LncRNAs whose deregulation is related to first line chemotherapeutic agents in
708 ovarian cancer.

709

710 **Figure legend**

711

712 **Figure1:** Mechanisms of action of lncRNAs. In the nucleus lncRNAs can act as (A) scaffold
713 for several protein complexes, (B) as guide for proteins or (C) as decoy for transcription
714 factors. In the cytoplasm lncRNAs can bind (D) in the 5'UTR region of mRNAs to upregulate
715 translation, (E) in the 3'UTR region of mRNAs in ALU repeats to destabilize mRNAs or (F)
716 can compete for the binding of endogenous miRNAs and keep them away from mRNA
717 targets.

718

719 **Highlights**

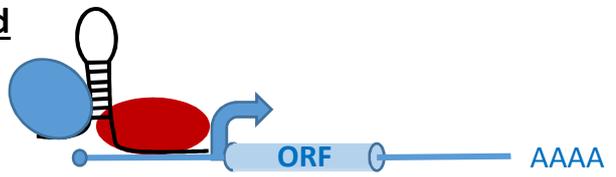
720 - Ovarian cancer is the leading cause of death from gynecological malignancies

721 - Resistance to treatment is the major cause of therapeutic failure

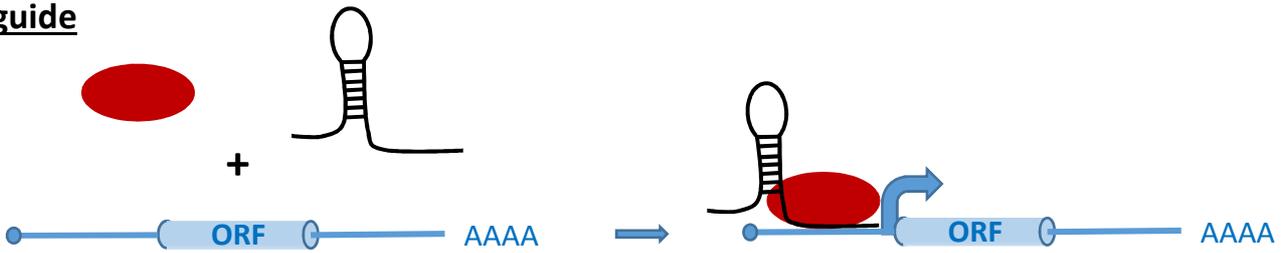
- 722 - LncRNAs act as oncogene or tumor suppressors and are involved in the response to
723 treatment
- 724 - LncRNAs expression levels might predict response to treatment
- 725 - Understanding lncRNAs modes of action could reveal innovative therapeutic strategies

NUCLEUS

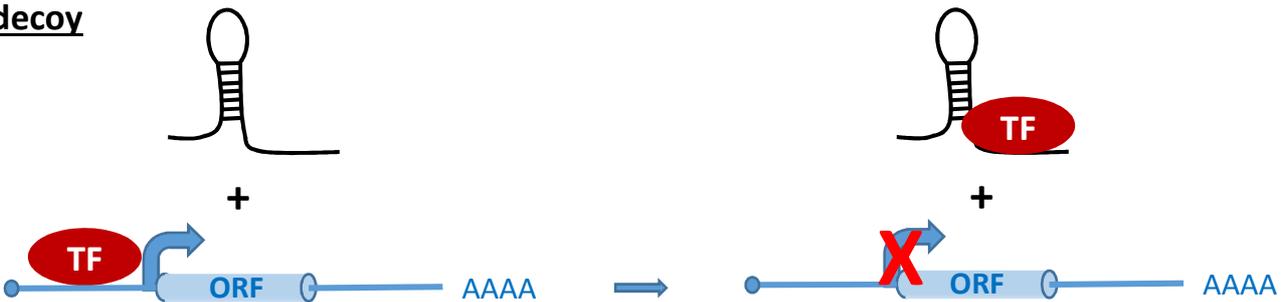
A scaffold



B guide

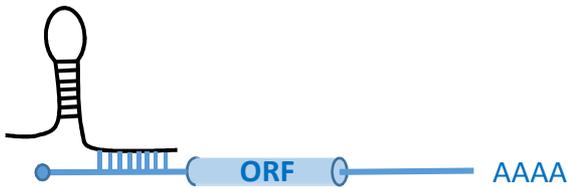


C decoy

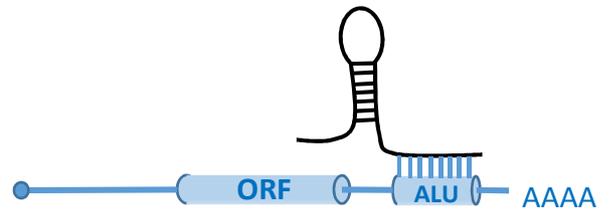


CYTOPLASM

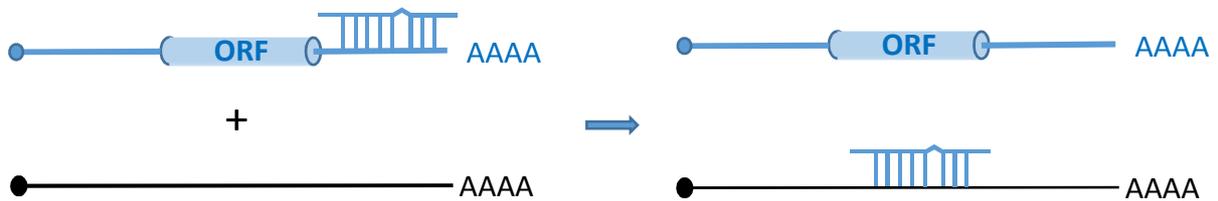
D upregulates translation



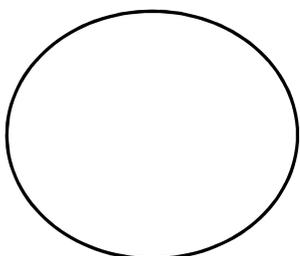
E destabilizes mRNA



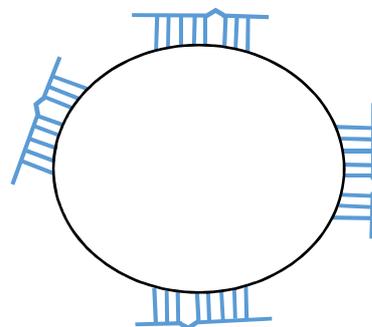
F endogenous competition for miRNA binding



or



or



Therapeutic Molecule	LncRNA	Up- or Down-regulation promotes resistance	Mechanism of action	References
Platinum salts	UCA1	up	Upregulates SRPK1 and Bcl-2, downregulates Bax, Caspases 3 and 9. Mechanism unknown	21
	HOTAIR	up	Activates Wnt/b-Catenin pathway. Mechanism unknown	27
	PVT1	up	Downregulates Caspase 3. Mechanism unknown	32
	PVT1	down	Downregulates P53 and TIMP1. Mechanism unknown	34
	XIST	down	Downregulates PTEN by releasing miR-214-3p	36
	H19	up	Upregulates glutathione metabolism. Mechanism unknown	39
	BC200	down	Mechanism unknown	41
Taxanes	UCA1	up	Upregulates ABCB1 by sponging miR-129	20
	NEAT1	up	Upregulates ZEB1 by sponging miR-194	42
	FER1L4	down	Activates MAPK signaling pathway. Mechanism unknown	45