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Ovarian cancer and KiSS-1 gene expression: A consideration of the use of Kisspeptin plus Kisspeptin aptamers in diagnostics and therapy.

¹Navinder Singh, ²Richard Hutson, ³Nathaniel G.N. Milton, ¹Farideh A. Javid

¹Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Huddersfield HD1 3DH, United Kingdom

² St James's Leeds University Teaching Hospital, Beckett Street, Leeds, LS9 7TF, United Kingdom

³ Centre for Biomedical Science Research, School of Health, Leeds Beckett University, City Campus, Leeds LS1 3HE, United Kingdom

Corresponding author: Dr Farideh Javid, Department of Pharmacy, University of Huddersfield, HE1 3DH, United Kingdom

Email: fajavid@hud.ac.uk

Tel: 0044 (0)1484 472543

Abstract

Gynaecological cancers continue to present a significant health burden upon the health of the global female population. This deficit is most prominent with ovarian cancer which possesses the lowest survival rate compared to all other cancers occurring within this anatomical region, with an annual UK-mortality of 7,300. The poor tolerability and selectivity of the treatment options that are currently available is likely to have contributed to this high mortality rate thus, demonstrating the need for the development of enhanced therapeutic approaches. Aptamer technology would involve the *engineering* of specifically sequenced oligonucleotide chains, which bind to macromolecular targets with a high degree of affinity and selectivity. Recent *in-vitro* studies conducted upon the clinical utility of this technique have supported its superiority in targeting individual therapeutic drug targets compared to various other targeting moieties currently within therapeutic use such as, monoclonal antibodies. For this reason, the employment of this technique is likely to be favourable in reducing the incidence of non-specific, chemotherapy-associated adverse effects. Kisspeptin is a naturally expressed polypeptide with an established role in the development of the reproductive system and other proposed roles in influencing the ability of ovarian cancer growths to exhibit the metastasis hallmark. This distinctive feature would indicate the potential for the manipulation of this pathway through the application of aptamer structures in developing a novel prophylactic strategy and improve the long-term outcome for ovarian cancer patients.

Key words Aptamer . Oligonucleotide . Ovarian Cancer . Anti-cancer . Kisspeptin . KISS

1. Introduction

Ovarian cancer can result from various abnormal growth of tissues originated from the fallopian tubes, uterus, cervix, and the superior area of the vagina and not just from ovaries. The current epidemiological figures have demonstrated ovarian cancer to possess the lowest survival rate compared to all other gynaecological cancers, with the condition being estimated to possess an annual mortality of 184,799 deaths globally (Bray et al., 2018). Ovarian cancer has been classified as the 6th most common cancer affecting UK-resident females and is estimated to possess an annual national mortality and morbidity equating to 4,227 and 7,300 respectively (Office of National Statistics, 2018). It is also indicated as the second most common malignancy after breast cancer in women over the age of 40 particularly in developed countries (Vargas, 2014). The mortality rate has not significantly changed in the past 30 years. 90% of patients diagnosed at stage I and II have a 5- year survival rate of 90% and 80%, respectively and this is significantly reduced to 25% when diagnosed at stage III and IV. Due to the lack of an accurate and reliable screening tool and vague symptoms over 70% of ovarian cancers are only diagnosed at stage III and IV and less than half of patients survive after 5 years of diagnosis (National Cancer Institute, 2018; Chien and Poole, 2018; Bowtell and Christie, 2017; Bhoola and Hoskins, 2006). The risk of developing ovarian carcinomas increases with age and women are most at risk between the age of 50 and 70 years. Younger women under the age of 30 years rarely develop the disease (National Cancer Institute, 2018; American Cancer Society, 2018; Foong and Bolton, 2017). The objectives of this review article were to gain a greater insight into the therapies available for the treatment of ovarian cancers, and the potential benefits of considering the emerging evidence base surrounding aptamer technology and the Kisspeptin biochemical pathway in the development of new therapeutic strategies to improve the long-term outcomes of patients diagnosed with this condition.

2. Information sources:

The PubMed electronic database between 2004 and 2021 was consulted to gain an insight into the current advances of aptamer technology and the therapeutic potential of its use against ovarian cancer. In order to focus the effort upon evaluating the recent advances within this field, the literature search was restricted to only consider studies conducted within 2004 and 2021, with the exception of historical discoveries. This search was further expanded

through applying a manual process of reference analysis of each of the articles identified from the initial search.

3. Searching:

The electronic database search conducted had identified 42562 studies (PubMed/Medline) using the following search terms: (Aptamer OR Aptasensor OR Aptamer-targeted imaging OR targeted delivery OR aptamer-radiolabelling) AND (Cancer OR Kisspeptin OR ovarian cancer). Furthermore, an additional 94 information sources were individually identified through reference analysis and evidence-led investigation and thus, incorporated into this study. Through manually assessing the titles and abstracts of the studies initially identified, it had allowed for early exclusion of clearly irrelevant literature from this research. The eligibility of the remaining studies for incorporation into this research document were evaluated using the PRISMA checklist. A total of 42,533 studies were excluded from being incorporated into this systematic review and this led to 118 articles which were included in this review (**Fig. 1**). The vast majority of the studies incorporated into this review were conducted within North America and Europe.

4. Study Selection

The inclusion criteria were designed to assist in the identification of valid studies for consideration in regard to the research question prior to the application of the PRISMA checklist. This selection process involved assessing each study against 3 criteria. (1) Randomised controlled trials, systematic reviews, meta-analysis studies and observational (prospective and retrospective) studies; (2) Use of cancer-focused Kisspeptin and KiSS-1 expression studies; (3) Oligonucleotide aptamer studies used.

5. Background of ovarian cancer

5. Ovarian cancer

Approximately 5% of all ovarian cancers are derived from non-epithelial cells such as germ cells and sex-cord-stromal cells. Ovarian cancers derived from epithelial cells are the most

common type and can be divided into type 1 and type 2. Type 1 cancers consist of low-grade serous carcinoma, clear cell, mucinous and endometrioid, whilst type 2 cancers include high-grade serous carcinomas (HGSCs) and are the most common type comprising 70%-80% of all epithelial ovarian cancers (Kurman and Shih, 2016). Type I carcinomas are suggested to be caused by inflammation, endometriosis and continued ovulation cycles. Type I cancers have a good prognosis as they are confined to the uterus at the time of diagnosis and have a low rate of recurrence of approximately 20% (Morice et al., 2016). 5%-15% of all epithelial ovarian cancers are derived from endometriosis which have a better outcome than the types that are not originated from endometriosis. Type II tumours which are more associated with significantly higher mortality rates and are often diagnosed late with poor prognosis, generally affect older women, and have higher rates of recurrence of approximately 50% with much lower survival rate of 5 years (Morice et al., 2016). Type II tumours are linked to genetic mutations of genes such as BRCA and p53, RAD51D, RAD51C, BRIP1 and to a lesser extent HNPCC genes and certain transcription factors such as HOX, MYC, FOXM1, PAX8 and MECOM (Chen and Berek, 2018; Tung and Garber, 2018; Antoniou et al., 2003; Norquist et al., 2016; Geary et al., 2008; Watson et al., 2001, Nameki et al., 2021).

The employment of surgical, radiotherapeutic and chemotherapeutic techniques would constitute as the main strategies used to treat cancer (Sullivan et al., 2015; Cancer Research UK, 2018). The provision of carboplatin as a six-cycle drug therapy is recommended as a first-line treatment for patients diagnosed with stage I ovarian cancer growths, this treatment would be substituted with paclitaxel in more progressed cases (Stage II-IV) (NICE, 2011) (Table 1). An open-label, randomized phase 3 trial (n=692) had evaluated the efficacy of the paclitaxel drug therapy at a weekly and 3-weekly dosage had concluded that the progression-free survival rate achieved to be not statistically significant between each of the treatment regimens (Chan et al., 2016). In more advanced stages of the disease surgical debulking is followed by chemotherapy. Platinum doublet therapy with usually paclitaxel either intraperitoneally or intravenously for 6 cycles has been the standard care for years (Jelovac and Armstrong, 2011). Although in majority of the patients a complete clinical response is achievable however, the rates of recurrence are high and can vary depending on the stage of the disease. For example, patients with stage III and higher have an approximately 70% chance of recurrence within two years of diagnosis (Ozols et al., 2003). Re-treatment with the platinum- based doublet therapy will be employed if the symptoms recur. In patients resistant to platinum therapy recurrence happens before 6 months after the last dose of platinum treatment. The treatment options for these patients are pegylated liposomal doxorubicin, gemcitabine, topotecan or paclitaxel alone

or in combination with bevacizumab (Pujade-Lauraine, et al., 2014). Patients who initially go through debulking surgery followed by chemotherapy with positive clinical response might also go through maintenance therapy (Table 1). The current maintenance therapies include the use of targeted therapies such as poly(ADP-ribose) polymerase (PARP) inhibitors such as Olaparib, rucaparib, and niraparib, or angiogenesis inhibitors such as bevacizumab alone or in combination (Gonzalez-Martin et al., 2019; Lin et al., 2021; Gogineni et al., 2021). Although the targeted therapies recently approved as the effective maintenance therapies however, they are not devoid of adverse effects. For example, PARP inhibitors, which disrupt the DNA repair mechanisms, such as olaparib that was used in BRCA mutant platinum -sensitive advanced or high-grade ovarian cancer induced haematological abnormalities such as anaemia, neutropenia, and thrombocytopenia (LaFargue, et al., 2019). In addition, there was also a risk of developing myelodysplastic syndromes and acute myeloid leukaemia (AstraZeneca, 2020; GlaxoSmithKline, 2020).

Despite the therapeutic advantages gained through the inclusion of monoclonal antibodies in numerous oncological treatment guidelines, these benefits did not replicate across all cancer types; with a relatively poor level of efficacy being seen in patients suffering from gynaecological cancers (Burstein, 2005). This could have been due to the physiology of ovarian cancer cells compared to those of other cancer types, in which monoclonal antibody therapy has demonstrated greater success. It was known that a significant proportion of breast cancers are associated with an overexpression of the human epidermal growth factor receptor (HER2) protein and therefore, would be more susceptible to the actions of an anti-HER2 monoclonal antibody such as Trastuzumab, that was engineered to target and inhibit the HER2 receptor site (Burstein, 2005; Romond et al., 2005; Chames et al., 2009). With consideration of the mechanism of trastuzumab, it is clear that the efficacy of this therapy relies largely upon the cancer cells overexpressing the HER2 receptors to promote its further proliferation. This mechanism is likely to be responsible for the variation in the treatment's efficacy between both breast and ovarian cancer, as the HER2 receptor overexpression exhibited by each of these cancer types is seen to present in approximately 30% and 11% of the total cases respectively (Burstein, 2005; Mitri et al., 2012). This is supported by another study which found that trastuzumab failed to demonstrate a significant improvement in those suffering from ovarian cancer when used as a single agent and suggested that its efficacy may be enhanced in combination with other traditional chemotherapy agents (Mabuchi and Kimura , 2010).

However, some years later the FDA approved an angiogenesis inhibitor, bevacizumab, a monoclonal antibody, to the chemotherapy regimens in platinum-sensitive or resistant

recurrent ovarian carcinomas, as well as in the maintenance therapy which improved the progression-free survival in some phase III studies; although it did not significantly affect the overall survival (Pujade-Lauraine et al., 2014). However, some other phase III studies indicated an improvement in both the progression-free survival and overall survival (Coleman et al., 2017; Ruan et al., 2018).

In addition to the conflicting results associated with the beneficial effect of bevacizumab on overall survival from phase III clinical trials, it also became apparent that the use of this drug is also associated with some adverse effects such as hypertension, proteinuria, exfoliative dermatitis, renal haemorrhage. Furthermore, bevacizumab also increased the risk of development of non-gastrointestinal fistula formation, arterial thromboembolic events, and nephrotic syndrome and bowel perforation in ovarian cancer patients (Randall and Monk, 2010).

Another major drawback of the clinical use of monoclonal antibodies relates to their acceptability to the host's immune system and the risks of non-specific effects (Chames et al., 2009). Many of the murine-based antibodies synthesised at the initial stages of antibody development were observed to often stimulate the immune system of the patient shortly after their administration, leading to their quick destruction (Chames et al., 2009). Moreover, the necessary large-scale production of antibodies and extensive purification steps greatly contribute to their elevated production cost compared to conventional medicines. This requirement is coupled with the average effective dose of antibodies requiring 8-16 doses of 375mgmL^{-2} to achieve clinical efficacy, causing the health costs incurred for each patient receiving monoclonal antibody therapy to be deemed unaffordable by many of the lower economic classes (Chames et al., 2009). In addition, the large size and relatively high molecular weight of antibodies compared to conventional drug compounds can become problematic when considering the accessibility of these proteins into deeper regions of tumour growths, a disadvantage which is known to be a contributor to the limited efficacy of this drug class.

In summary, the above studies have demonstrated the current advances and clinical applications of this field of targeted pharmacotherapy as well as, the various factors limiting its efficacy within practice. With consideration of this and the rising morbidity of cancer, it is demonstrated that there is a strong need for the development of more efficient, targeting techniques to assist in improving the safety, tolerability, and selectiveness of the current chemotherapeutic agents.

6. Significance of the Kisspeptin pathway

KiSS-1 was originally identified as a human malignant melanoma metastasis suppressor gene localised on chromosome 1q32.1 (Lee et al., 1996), that encoded for the 54 amino acid metastatin peptide, which acted via the Kisspeptin receptor (KISS1R) to inhibit metastasis (Ohtaki et al., 2001). The term Kisspeptin is now used for the metastatin peptide and its derivatives that bind to KISS1R, also known as GPR54 (Kotani et al., 2001; Pinilla et al., 2012). The Kisspeptin peptides and the KISS1R plus associated mRNA are both found in the CNS (Gottsch et al., 2004; Kotani et al., 2001; Muir et al., 2001; Rometo et al., 2007). The biological activity of Kisspeptin is linked to the C-terminus of the 54 amino acid Kisspeptin, with shorter C-terminal fragments of 10, 13 and 14 amino acids (Kisspeptin-10, Kisspeptin-13 and Kisspeptin-14 respectively) retaining activity via the KISS1R to inhibit metastasis (Kotani et al., 2001; Pinilla et al., 2012).

The metabolism of the Kisspeptin by matrix metalloproteases (MMP) results in inactivation of the peptide in terms of its anti-metastatic action (Takino et al., 2003). However, recent studies have identified the Kissorphin peptides (Milton, 2012) which are Kisspeptin fragments that have lost the last 4 C-terminal residues required for KISS1R binding but are still able to activate both NPFF1 (GPR147) and NPFF2 (GPR74) receptors and exert biological actions (Milton 2012; Gibula-Tarłowska et al., 2017; Gibula-Tarłowska et al., 2019a; Gibula-Tarłowska et al., 2019b; Gibula-Tarłowska and Kotłinska, 2020). The generation of Kissorphins could be mediated via MMP processing of Kisspeptins. Some of the biological actions of Kissorphin peptides are shared with via the NPFF1 and NPFF2 receptors natural ligand Neuropeptide-FF (NPFF) and Kisspeptin peptides (Lyubimov et al., 2010; Oishi et al., 2010; Milton, 2012; Elhabazi et al., 2013). These actions of Kisspeptins and their metabolites the Kissorphins may be relevant to therapeutic use of Kisspeptins in an ovarian cancer setting. Similarly, studies have shown that antibodies against Kisspeptin can cross-react with NPFF (Iijima et al., 2011; Chilumuri et al., 2013), raising the possibility that immunoassay measurement of Kisspeptin could be influenced by natural NPFF levels. Immunoassays used to measure Kisspeptin 10 (Milton, et al., 2012) are known to use the same antibody as used by Chilumuri et al., (2013) and were shown to cross react synthetic NPFF plus Kissorphin derivatives. As such immunoassay determination of Kisspeptin as a potential marker in an ovarian cancer setting may not always reflect biologically active material and therefore not always be fully representative of the anti-metastatic activity of Kisspeptin present in patient samples.

Kisspeptin is a central regulator of the reproductive axis via stimulation of gonadotropin releasing hormone release (Holly et al., 2015). Depletion of either KiSS-1, Kisspeptins or the KISS1R is associated with several forms of infertility, such as isolated hypogonadotropic hypogonadism (IHH) and central precocious puberty (CPP) (Chan, 2013; Brioude et al., 2013; Gottsch et al., 2009; Miraoui et al., 2013). Mutations within the KiSS-1 and KISS1R genes also contribute to the presentation of either IHH or CPP (Lanfranco et al., 2005 ; Pallais et al., 2006). Kisspeptin influences the progression of several diseases including, Alzheimer's disease, Polycystic ovary syndrome (PCOS) and specific types of cancer (Vincenza et al., 2018; Milton et al., 2012; Murphy and LeVine, 2010). PCOS is linked to a range of metabolic symptoms and associated with changes in the reproductive hormones activated by kisspeptin (Kotani et al., 2001; Holly et al., 2015; Legro et al., 1999; Glueck et al., 2003; Dunaif et al., 1989; Elting et al., 2001; Holte et al., 1996; Diamanti-Kandarakis et al., 2007; Talbott et al., 2000; Valkenburg et al., 2008). Kisspeptin has a pathophysiological role in PCOS and may be a useful biomarker (De Assis Rodrigues et al., 2019; Yilmaz et al., 2014).

The Kisspeptin peptides influence the incidence of metastasis in several cancer types, including bladder, gastric and ovarian cancers (Beck and Welch, 2010; Ciaramella et al., 2018). Downregulation of KiSS-1 gene expression is associated with greater risk of distant metastasis in gastric cancer (Dhar et al., 2004) and has been demonstrated in more severe forms of bladder cancer (Sanchez-Carbayo et al., 2003). There are therefore suggestions that the KiSS-1 and KISS1R are potential targets for treatment of metastatic cancer (Vincenza et al., 2018). The anti-metastatic role of Kisspeptin involves an inhibitory effect upon cell invasion, motility and adhesion; all of which play key roles in the embryonic development thus, potentially influencing the reproductive potential of a female (Lee et al., 1996; Trevisan et al., 2018; Ohtaki et al., 2001). This proposition is further supported by the expression of both KiSS-1 and KISS1R genes at the ovary, ovarian duct and uterus, and the presence of significantly higher concentrations of Kisspeptin within pregnant females (Jayasena et al., 2014). The KiSS-1 gene mediates an anti-metastatic effect on ovarian cancerous tumours via a direct-action inhibiting protein kinase C in addition to inhibiting the detachment and migration of cancerous cells that are morphologically-adapted to undertake the epithelial-mesenchymal transition dissemination process (Jiang et al., 2005; Ciaramella et al., 2018). A clinical study investigating the association between the expression of a gene product of the KiSS-1 gene (Kisspeptin-54) and the prognosis of patients diagnosed with ovarian cancer had found patients expressing the greater levels of polypeptide macromolecule to possess a statistically significant reduction of presenting with microscopic residual tumours following surgical resection procedures

($p=0.0084$) (Stafford et al., 2007). A promising proposition in manipulating this biological pathway involved the exogenous administration of Kisspeptin-54. Despite the preliminary data not associating this intervention with the production of significant adverse effects, the reduced expression of the complimentary G-protein coupled receptor of this macromolecule (KISS1R) by the majority of cancerous growths was found to present a challenge in preserving the efficacy of this supplementary therapy *in-vivo* (Vincenza et al., 2018; Beck and Welch, 2010).

The increased expression of MMP's within cancerous growths not expressing the KiSS-1 gene could contribute to tissue invasion and metastasis (Hata et al., 2007; Zucker et al., 1993). The relationship between MMP and KiSS-1 expression has also been observed with the development of liver metastasis originating from colorectal cancer types with low KiSS-1 expression in patients with elevated MMP-9 (Nomura et al., 1995). Earlier evidence surrounding this interaction had also eluded the role of inhibiting MMP-2 and MMP-9, which would potentially prevent inactivation of the Kisspeptin, preserving the anti-metastatic effects (Zhu et al., 2015). The use of Kisspeptin as a novel biomarker in monitoring the development of tumour metastasis within patients has been suggested for ovarian cancer (Chen et al., 2016; Prentice et al., 2007), however the crossreactivity of inactive MMP processed forms in immunoassays needs to be overcome (Chilumuri et al., 2013; Milton, et al., 2012).

7. Aptamer technology

The use of aptamer technologies provides a potential solution to the cross-reactivity issues with antibodies plus a potential route to develop both diagnostic and therapeutic compounds. Nucleic acid aptamers are single stranded DNA- or RNA-based oligonucleotide structures that possess an ability to bind to their complementary target with a great degree of affinity and specificity (Famulok and Mayer, 2014; Garst et al., 2011; Ku et al., 2015; Lakhin et al., 2013; Ellington and Szostak, 1990; Tuerk and Gold, 1990). Using libraries of short random nucleic acid sequences combined with selection assays allows the identification of aptamers sequences that are specific for a target which could be used in both diagnostic and therapeutic settings. The main methods for doing this involve the application of the Systematic Evolution of Ligands by EXponential enrichment (SELEX) process (Hori et al., 2018). Using a library with fixed primer regions at the 5' and 3' ends of the random sequences, the target protein can then be used to pull down binding aptamers which can then be amplified through the repeated application of the Polymerase Chain Reaction PCR) (Darmostuk et al., 2015). This process would allow the selection of specific Kisspeptin binding aptamers (**Fig. 2**). A range of selection

processes can be employed so for example with raising KISS1R specific aptamers it may be necessary to use Whole Cell SELEX, which would utilise the KISS1R target proteins present upon the membrane of living cells within an environment that resembles the structure *in-vivo* to a greater extent (Chauveau et al., 2007; Liu et al., 2009; Ohuchi, 2012). Aptamers can also be used in the development of sensors for disease monitoring, detection of pollutants and the drug discovery process (Bhalla et al., 2016). Aptamer based biosensors or ‘aptasensors’ are known to be superior in their accuracy compared to those employing monoclonal antibodies, due conformational changes during the binding of the aptamer to the target (Morita et al., 2018). There are many different types of aptasensors used within clinical study with one of the most notable involving the incorporation of an electrochemical molecule. This technique involved chemically bonding an aptamer bioreceptor to an electrode surface to which an analyte would be presented and retained. Following this, the aptamer-analyte complex would be exposed to a secondary aptamer molecule that would be targeted to bind to a different site on the surface of the analyte thus, producing an aptamer-analyte-aptamer complex often termed as an ‘Aptamer sandwich’ (Fig. 3). The secondary aptamer molecule is often conjugated with another charged species such as, gold nanoparticles, which would be detected by the electrode (Pavlov et al., 2004). Earlier detection of ovarian cancer growths using aptasensors has shown the strength of this technology in the ovarian cancer diagnostic field for the detection of CA125 (Hamd-Ghadareh et al., 2017) and there is the potential to apply similar strategies for detection of Kisppeptin or the KISS1R.

The use of aptamers for both diagnostic and therapeutic purposes would require the consideration of several factors such as, the relatively short shelf life, chemical stability and delivery strategies to ensure the aptamers are able to reach their molecular target. Currently, the use of base and backbone modification of the aptamer structure have demonstrated positive results in improving the stability of aptamer molecules thus, allowing them to become practical within a healthcare setting (Hori et al., 2018; Famulok et al., 2007; Hassanzadeh et al., 2018). Aptamer delivery into the central nervous system can also be achieved through the application of various techniques including, the entrapment of aptamer molecules into liposomes and protein transduction domains, and the manipulation of nanoparticles (Cheng et al., 2013; Koffie et al., 2011), this has been used with aptamers against targets relevant to Alzheimer’s disease (Huiyu et al., 2015).

The use of aptamers has also displayed promise in optimising the current anti-cancer treatments through providing a potentially novel route in delivering these chemotherapeutic agents to cancerous growths at a great selectively and more cost-effective manner compared to

other targeting moieties that are currently used within practice notably, monoclonal antibodies. As mentioned previously, aptamer molecules possess a much higher degree of specificity in their binding to a molecular target compared to other targeting moieties. When coupled with the reduced cost incurred in aptamer production and the wide acceptability of targets ranging from small chemical mediators to entire cells, it is clear that their use within biosensor technology would be advantageous (Hori et al., 2018). A recent review of aptamers for use in ovarian cancer diagnosis and treatment has highlighted aptamers to known cancer markers such as CA125, CA70 plus HER2 for potential therapeutic use and CA125 for potential diagnostic use (Ruan & Li, 2021).

8. Strategies

Kisspeptin and KISS1R for ovarian cancer therapeutic plus diagnostic targeting are viable options based on the observations for the biological activities of Kisspeptin in relation to inhibitory effects on metastasis via activation of KISS1R. The multiple forms of Kisspeptins (Kotani et al., 2001; Pinilla et al., 2012) and the cross-reactivity of other peptides plus inactive metabolites (Iijima et al., 2011; Milton et al 2012; Milton, 2012; Chilumuri et al., 2013) cause potential problems in using immunoassays for diagnosis or therapy monitoring. A solution to this may be to use aptamer technologies and select specific aptamers with both positive and negative selection strategies to effectively identify Kisspeptin specific aptamers that are suitable for diagnostic use. It is clear from recent studies that diagnosis is likely to need multiple measures (Menon et al., 2021) rather than just Kisspeptin levels, for example a combination of Kisspeptin with known tumour markers (Chen et al., 2016).

The pharmacokinetic and pharmacodynamic properties of Kisspeptin and synthetic KISS1R agonists in humans (Abbara et al., 2020) raise the possibility of using such compounds in an ovarian cancer setting. Aptamers that act as receptor ligands show potential in cancer therapy (Zhang et al., 2021). Specific aptamers against the KISS1R may also offer potential and may help to rule out biological actions at other receptors such as the NPFF1 and NPFF2 which respond to Kisspeptin. Allosteric aptamers have been shown to enhance receptor activation by insulin (Yunn et al., 2021) and this approach may also provide a mechanism to enhance Kisspeptin activity. Peptide aptamers with structural similarities to Kisspeptin may also offer potential in this setting. A major advantage of using Kisspeptin itself is that it is an endogenous peptide and therefore less likely to be seen as foreign by the body and trigger an unwanted immune response. A disadvantage of Kisspeptin is the observation of desensitization

of KISS1R by repeated administration of Kisspeptin 10 (Seminara et al., 2006) and there is evidence of KISS1R downregulation in some cancer settings (Ly et al., 2020). There is also evidence of antimetastatic actions of Kisspeptin that are independent of KISS1R and these areas require further study (Ly et al., 2020).

The use of specific aptamers which have a high affinity for the Kisspeptin would allow for the more selective targeting of this molecular target within cancer pathophysiological mechanisms and reduce the incidence of a non-specific blockade of other chemical mediators or the blockade of Kisspeptin in a different signalling pathway, each of which could facilitate the production of adverse effects within the patient. For this reason, their application in ovarian cancer therapeutic strategies would be largely advantageous in the clinical management of these conditions and warrants further research.

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N.G.N.M. is named as the inventor on a UK patent held by the University of Roehampton for the use of kissorphan peptides to treat Alzheimer's disease, Creutzfeldt-Jakob disease or diabetes mellitus (Publication Numbers: GB2493313 B); under the University of Roehampton rules he could benefit financially if the patent is commercially exploited. N.G.N.M. is also a shareholder and director of NeuroDelta Ltd (Company No: 06222473; <https://www.bioinformatics-protocols.com/Neurodelta/>). This does not alter our adherence to the journal policies. The reference for this patent is: Milton, N. (2017) Kissorphan peptides for use in the treatment of Alzheimer's disease, Creutzfeldt-Jakob disease or diabetes mellitus. United Kingdom Patent Publication Number GB 2493313 (B).

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9. References

1. Abbara A, Eng PC, Phylactou M, Clarke SA, Richardson R, Sykes CM, Phumsatitpong C, Mills E, Modi M, Izzi-Engbeaya C, Papadopoulou D, Purugganan K, Jayasena CN, Webber L, Salim R, Owen B, Bech P, Comminos AN, McArdle CA, Voliotis M, Tsaneva-Atanasova K, Moenter S, Hanyaloglu A, Dhillon WS. Kisspeptin receptor agonist has therapeutic potential for female reproductive disorders. *J Clin Invest.* 2020; **130**(12): 6739-6753.

2. American Cancer Society. Cancer facts and figures 2018. Special Section: Ovarian Cancer. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-special-section-ovarian-cancer-2018.pdf>
3. Antoniou A, Pharoah PDP, Narod S, *et al.* Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003; **72**: 1117–30.
4. AstraZeneca. Olaparib package insert. 2020.
5. Beck BH, Welch DR. The KISS1 metastasis suppressor: A good night kiss for disseminated cancer cells. *Eur J Cancer* 2010; **46**: 1283–9.
6. Bhalla N, Jolly P, Formisano N, Estrela P. Introduction to biosensors. *Essays Biochem* 2016; **60**: 1–8.
7. Bhoola S, Hoskins WJ. Diagnosis and Management of Epithelial Ovarian Cancer. *Obstet Gynecol* 2006; **107**: 1399-410. https://journals.lww.com/greenjournal/Fulltext/2006/06000/Diagnosis_and_Management_of_Epithelial_Ovarian.29.aspx.
8. Bowtell DDL, Christie EL. Acquired chemotherapy resistance in ovarian cancer. *Ann Oncol* 2017; **28**: viii13–5.
9. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394–424.
10. Brioude F, Bouligand J, Francou B, *et al.* Two families with normosmic congenital hypogonadotropic hypogonadism and biallelic mutations in KISS1R (KISS1 receptor): clinical evaluation and molecular characterization of a novel mutation. *PLoS One* 2013; **8**: e53896.
11. Burstein HJ. The Distinctive Nature of HER2-Positive Breast Cancers. *N Engl J Med* 2005; **353**: 1652–4.
12. Cancer Research UK. Treatment for cancer. 2017; Released **2018**. <https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment>.
13. Chames P, Van Regenmortel M, Weiss E, Baty D. Therapeutic antibodies: successes, limitations and hopes for the future. 2009; **157**: 220–33.

14. Chan JK, Brady MF, Penson RT, *et al.* Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer. *N Engl J Med* 2016; **374**: 738–48.
15. Chan YM. Effects of Kisspeptin on Hormone Secretion in Humans. In: Kauffman A., Smith J. (eds) Kisspeptin Signaling in Reproductive Biology. Advances in Experimental Medicine and Biology, 2013; vol **784**. Springer, New York, NY.
 - a. https://doi.org/10.1007/978-1-4614-6199-9_5.
16. Chauveau F, Aissouni Y, Hamm J, *et al.* Binding of an aptamer to the N-terminal fragment of VCAM-1. *Bioorg Med Chem Lett* 2007; **17**: 6119–22.
17. Chen L., Berek, J. Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: epidemiology and risk factors. Available at: [Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors - UpToDate](#). 2021.
18. Chen L, Liu M, Ji J, Lin W, Shan F, Liu H. Diagnostic accuracy of peripheral blood Kisspeptin mRNA and plasma CA125 protein for detection of epithelial ovarian cancer in patients who have ever been pregnant. *Neoplasma*. 2016; **63**(6): 999-1006.
19. Cheng C, Chen YH, Lennox KA, Behlke MA, Davidson BL. In vivo SELEX for Identification of Brain-penetrating Aptamers. *Mol Ther Nucleic Acids* 2013; **2**: e67–e67.
20. Chien, J. and Poole, E. (2018). Ovarian cancer prevention, screening and early detection: report from the 11th Biennial Ovarian Cancer Research Symposium. *Int J Gynecol Cancer*, 2018, 27, S20-S22.
21. Chilumuri A, Ashioti M, Nercessian AN, Milton NG. Immunolocalization of Kisspeptin Associated with Amyloid- β Deposits in the Pons of an Alzheimer's Disease Patient. *J Neurodegener Dis*. 2013; **2013**: 879710.
22. Ciaramella V, Della Corte CM, Di Mauro C, *et al.* Antitumor efficacy of Kisspeptin in human malignant mesothelioma cells. *Oncotarget* 2018; **9**: 19273–82.
23. Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL. *et al.* Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017; **18**: 779–91.
24. Darmostuk M, Rimpelova S, Gbelcova H, Ruml T. Current approaches in SELEX: An update to aptamer selection technology. *Biotechnol Adv* 2015; **33**: 1141–61.
25. De Assis Rodrigues NP, Laganà AS, Zaia V, *et al.* The role of Kisspeptin levels in polycystic ovary syndrome: a systematic review and meta-analysis. *Arch Gynecol Obstet* 2019; **300**: 1423—1434.

26. Dhar DK, Naora H, Kubota H, *et al.* Downregulation of KiSS-1 expression is responsible for tumor invasion and worse prognosis in gastric carcinoma. *Int J Cancer* 2004; **111**: 868–72.
27. Diamanti-Kandarakis E, Papavassiliou AG, Kandarakis SA, Chrousos GP. Pathophysiology and types of dyslipidemia in PCOS. *Trends Endocrinol Metab* 2007; **18**: 280–5.
28. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 1989; **38**: 1165–74.
29. Elhabazi K, Humbert JP, Bertin I, Schmitt M, Bihel F, Bourguignon JJ, Bucher B, Becker JA, Sorg T, Meziane H, Petit-Demoulière B, Ilien B, Simonin F. Endogenous mammalian RF-amide peptides, including PrRP, kisspeptin and 26RFa, modulate nociception and morphine analgesia via NPFF receptors. *Neuropharmacology*. 2013; **75**: 164-71.
30. Ellington AD, Szostak JW. In vitro selection of RNA molecules that bind specific ligands. *Nature* 1990; **346**: 818–22.
31. Elting MW, Korsen TJM, Bezemer PD, Schoemaker J. Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. *Hum Reprod* 2001; **16**: 556–60.
32. Famulok M, Mayer G. Aptamers and SELEX in Chemistry & Biology. *Chem Biol* 2014; **21**: 1055–8.
33. Famulok M, Hartig JS, Mayer G. Functional Aptamers and Aptazymes in Biotechnology, Diagnostics, and Therapy. *Chem Rev* 2007; **107**: 3715–43.
34. Foong KW, Bolton H. Obesity and ovarian cancer risk: A systematic review. *Post Reprod Heal* 2017; **23**: 183–98.
35. Garst AD, Edwards AL, Batey RT. Riboswitches: structures and mechanisms. *Cold Spring Harb Perspect Biol* 2011; **3**: a003533.
36. Geary J, Sasieni P, Houlston R, Izatt L, Eeles R. (2008). Gene-related cancer
 - a. spectrum in families with hereditary non-polyposis colorectal cancer (HNPCC). *Fam Cancer*; **7**(2):163-72.
37. Geogineni, V., Morand, S., Staats, H., Royfman, R., Devanaboyina, M., Elinloth, K. et al., Current overaian cancer maintenance strategies and promising new developments. *J Cancer*, 2021, 12(1): 38-53.

38. Gibula-Bruzda E, Marszalek-Grabska M, Gawel K, Trzcinska R, Silberring J, Kotlinska JH. The new kisspeptin derivative - kissorphin (KSO) - attenuates acute hyperlocomotion and sensitization induced by ethanol and morphine in mice. *Alcohol*. 2017; **64**: 45-53.
39. Gibula-Tarlowska E, Grochecki P, Silberring J, Kotlinska JH. The kisspeptin derivative kissorphin reduces the acquisition, expression, and reinstatement of ethanol-induced conditioned place preference in rats. *Alcohol*. 2019a; **81**: 11-19
40. Gibula-Tarlowska E, Kedzierska E, Piechura K, Silberring J, Kotlinska JH. The influence of a new derivate of kisspeptin-10 - Kissorphin (KSO) on the rewarding effects of morphine in the conditioned place preference (CPP) test in male rats. *Behav Brain Res*. 2019b; **372**: 112043.
41. Gibula-Tarlowska E, Kotlinska JH. Kissorphin improves spatial memory and cognitive flexibility impairment induced by ethanol treatment in the Barnes maze task in rats. *Behav Pharmacol*. 2020; **31**(2&3): 272-282.
42. GlaxoSmithKline. Niraparib package insert. 2020.
43. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR. et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine*. 2019; 381:2391–402.
44. Gottsch ML, Clifton DK, Steiner RA. From KISS1 to Kisspeptins: An historical perspective and suggested nomenclature. *Peptides* 2009; **30**: 4–9.
45. Gottsch ML, Cunningham MJ, Smith JT, et al. A Role for Kisspeptins in the Regulation of Gonadotropin Secretion in the Mouse. *Endocrinol*; 2004, **145**: 4073–7.
46. Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. *Metabolism* 2003; **52**: 908–15.
47. Hamd-Ghadareh S, Salimi A, Fathi F, Bahrami S. An amplified comparative fluorescence resonance energy transfer immunosensing of CA125 tumor marker and ovarian cancer cells using green and economic carbon dots for bio-applications in labeling, imaging and sensing. *Biosens Bioelectron* 2017; **96**: 308–16.
48. Hanahan D, Weinberg RA. The Hallmarks of Cancer. *Cell* 2000; **100**: 57–70.
49. Hassanzadeh L, Chen S, Veedu RN. Radiolabeling of Nucleic Acid Aptamers for Highly Sensitive Disease-Specific Molecular Imaging. *Pharmaceuticals (Basel)* 2018; **11**: 106.
50. Hata K, Dhar DK, Watanabe Y, Nakai H, Hoshiai H. Expression of metastin and a G-

- protein-coupled receptor (AXOR12) in epithelial ovarian cancer. *Eur J Cancer* 2007; **43**: 1452–9.
51. Holly C, Waljit SD, Channa NJ. Comprehensive Review on Kisspeptin and Its Role in Reproductive Disorders. *Endocrinol Metab* 2015; **30**: 124–41.
 52. Holte J, Gennarelli G, Berne C, Bergh T, Lithell H. Elevated ambulatory day-time blood pressure in women with polycystic ovary syndrome: a sign of a pre-hypertensive state? *Hum Reprod* 1996; **11**: 23–8.
 53. Hori S-I, Herrera A, Rossi J, Zhou J. Current Advances in Aptamers for Cancer Diagnosis and Therapy. *Cancers (Basel)* 2018; **10**: 9.
 54. Huiyu L, Yusheng S, Zhewen K, *et al.* Inhibition of BACE1 Activity by a DNA Aptamer in an Alzheimer's Disease Cell Model. *PLoS One* 2015; **10**: e0140733.
 55. Iijima N, Takumi K, Sawai N, Ozawa H. An immunohistochemical study on the expressional dynamics of kisspeptin neurons relevant to GnRH neurons using a newly developed anti-kisspeptin antibody. *J Mol Neurosci.* 2011; **43**(2): 146-54.
 56. Jayasena CN, Abbara A, Izzi-Engbeaya C, *et al.* Reduced levels of plasma Kisspeptin during the antenatal booking visit are associated with increased risk of miscarriage. *J Clin Endocrinol Metab* 2014; **99**: E2652–60.
 57. Jelovac D, Armstrong DK (2011). Recent progress in the diagnosis and treatment of ovarian cancer. *CA Cancer J Clin.* 2011, May-Jun; 61(3):183-203.
 58. Jiang Y, Berk M, Singh LS, Tan H, Yin L, Powell CT, Xu Y. KiSS1 suppresses metastasis in human ovarian cancer via inhibition of protein kinase C alpha. *Clin Exp Metastasis.* 2005; **22**(5): 369-76
 59. Koffie RM, Farrar CT, Saidi L-J, William CM, Hyman BT, Spires-Jones TL. Nanoparticles enhance brain delivery of blood-brain barrier-impermeable probes for in vivo optical and magnetic resonance imaging. *Proc Natl Acad Sci U S A* 2011; **108**: 18837–42.
 60. Kotani M, Detheux M, Vandenberghe A, *et al.* The metastasis suppressor gene KiSS-1 encodes Kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. *J Biol Chem* 2001; **276**: 34631.
 61. Ku T-H, Zhang T, Luo H, *et al.* Nucleic Acid Aptamers: An Emerging Tool for Biotechnology and Biomedical Sensing. *Sensors (Basel)* 2015; **15**: 16281–313.
 62. Kurman R. J., Shih I. M. The Dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. *Am J. Pathol.*, 2016, 186:733-747.

63. LaFargue C. J., Dal Molin G. Z., Sood A. K., Coleman R. L. Exploring and comparing adverse events between PARP inhibitors. *Lancet Oncol.* 2019, 20(1), e15-e28.
64. Lakhin A V, Tarantul VZ, Gening L V. Aptamers: problems, solutions and prospects. *Acta Naturae* 2013; **5**: 34–43.
65. Lanfranco F, Gromoll J, von Eckardstein S, Herding EM, Nieschlag E, Simoni M. Role of sequence variations of the GnRH receptor and G protein-coupled receptor 54 gene in male idiopathic hypogonadotropic hypogonadism. *Eur J Endocrinol*; 2005, **153**: 845–52.
66. Lee J-H, Miele ME, Hicks DJ, *et al.* KiSS-1, a Novel Human Malignant Melanoma Metastasis-Suppressor Gene. *JNCI J Natl Cancer Inst* 1996; **88**: 1731–7.
67. Legro RS, Kunesman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999; **84**: 165–9.
68. Lin Q, Liu W, Xu S, Shang H, Li J, Guo Y. *et al.* PARP inhibitors as maintenance therapy in newly diagnosed advanced ovarian cancer: a meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology.* 2020; 00:1–9
69. Liu Y, Kuan C-T, Mi J, *et al.* Aptamers selected against the unglycosylated EGFRvIII ectodomain and delivered intracellularly reduce membrane-bound EGFRvIII and induce apoptosis. *Biol Chem* 2009; **390**: 137.
70. Ly, T., Harihar, S., & Welch, D. R. (2020). KISS1 in metastatic cancer research and treatment: potential and paradoxes. *Cancer metastasis reviews*, 39(3), 739–754.
71. Lyubimov Y, Engstrom M, Wurster S, Savola JM, Korpi ER, Panula P. Human kisspeptins activate neuropeptide FF2 receptor. *Neuroscience.* 2010; **170**(1): 117-22.
72. Mabuchi S, Kimura T. Treatment of ovarian cancer by monoclonal antibodies. *Discov Med* 2010; **9**: 197–203.
73. Maeda D., Shih I. M. Pathogenesis and the role of ARID1A mutation in endometriosis-related ovarian neoplasms. *Adv. Anat. Pathol.* 2013, 20: 45-52.
74. Mallen, A., Soong, T., Townsend, M., Wenham, R., Crum, C., Tworoger, S. (2018). Surgical prevention strategies in ovarian cancer. *Gynecol Oncol*, 2018, 151, 166-175.
75. Menon U, Gentry-Maharaj A, Burnell M, Singh N, Ryan A, Karpinskyj C, Carlino G, Taylor J, Massingham SK, Raikou M, Kalsi JK, Woolas R, Manchanda R, Arora R, Casey L, Dawnay A, Dobbs S, Leeson S, Mould T, Seif MW, Sharma A, Williamson K, Liu Y, Fallowfield L, McGuire AJ, Campbell S, Skates SJ, Jacobs IJ, Parmar M.

- Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet*. 2021; **397**(10290): 2182-2193.
76. Milton NG. In Vitro Activities of Kissorphin, a Novel Hexapeptide KiSS-1 Derivative, in Neuronal Cells. *J Amino Acids* 2012; **2012**: 691463.
 77. Milton NGN, Chilumuri A, Rocha-Ferreira E, Nercessian AN, Ashioti M. Kisspeptin prevention of amyloid- β peptide neurotoxicity in vitro. *ACS Chem Neurosci* 2012; **3**: 706–19.
 78. Miraoui H, Dwyer AA, Sykiotis GP, *et al*. Mutations in FGF17, IL17RD, DUSP6, SPRY4, and FLRT3 Are Identified in Individuals with Congenital Hypogonadotropic Hypogonadism. *Am J Hum Genet* 2013; **92**: 725–43.
 79. Mitri Z, Constantine T, O'Regan R. The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. *Chemother Res Pract* 2012; **2012**. DOI:10.1155/2012/743193.
 80. Morice, P., Leary, A., Creutzberg, C., Abu-Rustum, N., Darai, E. Endometrial cancer, *Lancet*, 2016, 387, 1094-1108.
 81. Morita Y, Kameyama H, Volk D, Tanaka T. Aptamer Therapeutics in Cancer: Current and Future. *Cancers (Basel)* 2018; **10**: 80.
 82. Muir AI, Chamberlain L, Elshourbagy N, *et al*. AXOR12, a Novel Human G Protein-coupled Receptor, Activated by the Peptide KiSS-1. *J Biol Chem* 2001; **276**: 28969–75.
 83. National Cancer Institute. Surveillance, Epidemiology, and End Results Programme. Cancer stat facts: ovarian cancer (2018). Ovarian Cancer — Cancer Stat Facts
 84. National Institute for Health and Care Excellence. Ovarian cancer: recognition and initial management. Clin. Guidel. [CG122]. 2011. <https://www.nice.org.uk/Guidance/cg122>.
 85. Nomura H, Sato H, Seiki M, Mai M, Okada Y. Expression of membrane-type matrix metalloproteinase in human gastric carcinomas. *Cancer Res* 1995; **55**: 3263.
 86. Norquist BM, Harrell M, Brady MF, Walsh T, Lee MK., *et al*. (2016). Inherited
 - a. mutations in women with ovarian carcinoma. *JAMA Oncology*; 2(4):482-90.
 87. Office of National Statistics. Cancer registration statistics, England Statistical bulletins. *Cancer Regist. Stat. Engl.* 2016. Released 4 June 2018. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/previousReleases>.

88. Ohtaki T, Shintani Y, Honda S, *et al.* Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. *Nature* 2001; **411**: 613–7.
89. Ohuchi S. Cell-SELEX Technology. In: Biores Open Access. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA, 2012: 265–72.
90. Oishi S, Misu R, Tomita K, Setsuda S, Masuda R, Ohno H, Naniwa Y, Ieda N, Inoue N, Ohkura S, Uenoyama Y, Tsukamura H, Maeda K, Hirasawa A, Tsujimoto G, Fujii N. Activation of Neuropeptide FF Receptors by Kisspeptin Receptor Ligands. *ACS Med Chem Lett.* 2010; **2**(1): 53–7.
91. Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA. *et al.* Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2003; **21**:3194–200.
92. Pallais JC, Bo-Abbas Y, Pitteloud N, Crowley WF, Seminara SB. Neuroendocrine, gonadal, placental, and obstetric phenotypes in patients with IHH and mutations in the G-protein coupled receptor, GPR54. *Mol Cell Endocrinol*; 2006, **254–255**: 70–7.
93. Pinilla L, Aguilar E, Dieguez C, Millar R, Tena-Sempere M. Kisspeptins and Reproduction: Physiological Roles and Regulatory Mechanisms. 2012; **92**: 1235.
94. Prentice LM, Klausen C, Kalloger S, Köbel M, McKinney S, Santos JL, *et al.* Kisspeptin and GPR54 immunoreactivity in a cohort of 518 patients defines favourable prognosis and clear cell subtype in ovarian carcinoma. *BMC Med.* 2007; **5**: 33.
95. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G. *et al.* Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol.* 2014, **32**:1302–8.
96. Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. *Gynecol Oncol.* 2010; **117**:497–504.
97. Rometo AM, Krajewski SJ, Lou Voytko M, Rance NE. Hypertrophy and Increased Kisspeptin Gene Expression in the Hypothalamic Infundibular Nucleus of Postmenopausal Women and Ovariectomized Monkeys. *J Clin Endocrinol Metab* 2007; **92**: 2744–50.
98. Romond EH, Perez EA, Bryant J, *et al.* Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. *N Engl J Med* 2005; **353**: 1673–84.

99. Ruan G., Ye L., Liu G., An J., Sehouli J. Sun P. The role of bevacizumab in targeted vascular endothelial growth factor therapy for epithelial ovarian cancer: an updated systemic review and met-analysis. *Onco Targets Ther.* 2018, 11: 521-528.
100. Ruan L, Li X. Applications of Aptamers in the Diagnosis and Treatment of Ovarian Cancer: Progress From 2016 to 2020. *Front Genet.* 2021; 12: 683542.
101. Sanchez-Carbayo M, Capodieci P, Cordon-Cardo C. Tumor suppressor role of KiSS-1 in bladder cancer: loss of KiSS-1 expression is associated with bladder cancer progression and clinical outcome. *Am J Pathol* 2003; **162**: 609–17.
102. Seminara, S. B., Dipietro, M. J., Ramaswamy, S., Crowley, W. F., Jr, & Plant, T. M. Continuous human metastatin 45-54 infusion desensitizes G protein-coupled receptor 54-induced gonadotropin-releasing hormone release monitored indirectly in the juvenile male Rhesus monkey (*Macaca mulatta*): a finding with therapeutic implications. *Endocrinology*, 2006, *147*(5), 2122–2126.
103. Stafford LJ, Vaidya KS, Welch DR. Metastasis suppressors genes in cancer. *Int J Biochem Cell Biol* 2008; **40**: 874–91.
104. Sullivan R, Alatisse OI, Anderson BO, *et al.* Global cancer surgery: delivering safe, affordable, and timely cancer surgery. *Lancet Oncol* 2015; **16**: 1193–224.
105. Takino T, Koshikawa N, Miyamori H, *et al.* Cleavage of metastasis suppressor gene product KiSS-1 protein/metastatin by matrix metalloproteinases. *Oncogene* 2003; **22**: 4617–26.
106. Talbott EO, Guzick DS, Sutton-Tyrrell K, *et al.* Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler Thromb Vasc Biol* 2000; **20**: 2414–21.
107. Trevisan CM, Montagna E, de Oliveira R, *et al.* Kisspeptin/GPR54 System: What Do We Know About Its Role in Human Reproduction? *Cell Physiol Biochem*; 2018, **49**: 1259–76.
108. Tuerk C, Gold L. Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. *Science* 1990; **249**: 505 – 510.
109. Tung NM, Garber JE. BRCA1/2 testing: therapeutic implications for breast cancer management. *Br J Cancer* 2018; **119**: 141–52.
110. Vargas, A. N. Natural history of ovarian cancer. *E Cancer Medical Science*, 2014, 8, 465.
111. Valkenburg O, Steegers-Theunissen RPM, Smedts HPM, *et al.* A more

- atherogenic serum lipoprotein profile is present in women with polycystic ovary syndrome: a case-control study. *J Clin Endocrinol Metab* 2008; **93**: 470–6.
112. Vincenza C, Carminia Maria Della C, Fortunato C, Floriana M. Kisspeptin and Cancer: Molecular Interaction, Biological Functions, and Future Perspectives. *Front Endocrinol (Lausanne)* 2018; **9**: article 115. DOI:10.3389/fendo.2018.00115.
113. Watson P, Butzow R, Lynch HT, Mecklin JP, Jarvinen HJ et al., (2001). The clinical features of ovarian cancer in hereditary nonpolyposis colorectal cancer. *Gynecol Oncology*; 82(2):223-228.
114. Yilmaz S., Kerimoglu O., Pekin A., et al. Metastin levels in relation with hormonal and metabolic profile in patients with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol*; 2014, **180**: 56–60.
115. Yunn NO, Park M, Park S, Lee J, Noh J, Shin E, Ryu SH. A hotspot for enhancing insulin receptor activation revealed by a conformation-specific allosteric aptamer. *Nucleic Acids Res.* 2021; **49**(2): 700-712.
116. Zhang N, Bing T, Shen L, Feng L, Liu X, Shangguan D. A DNA Aptameric Ligand of Human Transferrin Receptor Generated by Cell-SELEX. *Int J Mol Sci.* 2021; **22**(16): 8923.
117. Zhu C, Takasu C, Morine Y, et al. KISS1 Associates with Better Outcome via Inhibiting Matrix Metalloproteinase-9 in Colorectal Liver Metastasis. *Ann Surg Oncol* 2015; **22**: 1516–23.
118. Zucker S, Lysik RM, Zarrabi MH, Moll U. M(r) 92,000 type IV collagenase is increased in plasma of patients with colon cancer and breast cancer. *Cancer Res* 1993; **53**: 140.

Table 1. Recommended strategies for the treatment of ovarian carcinomas.

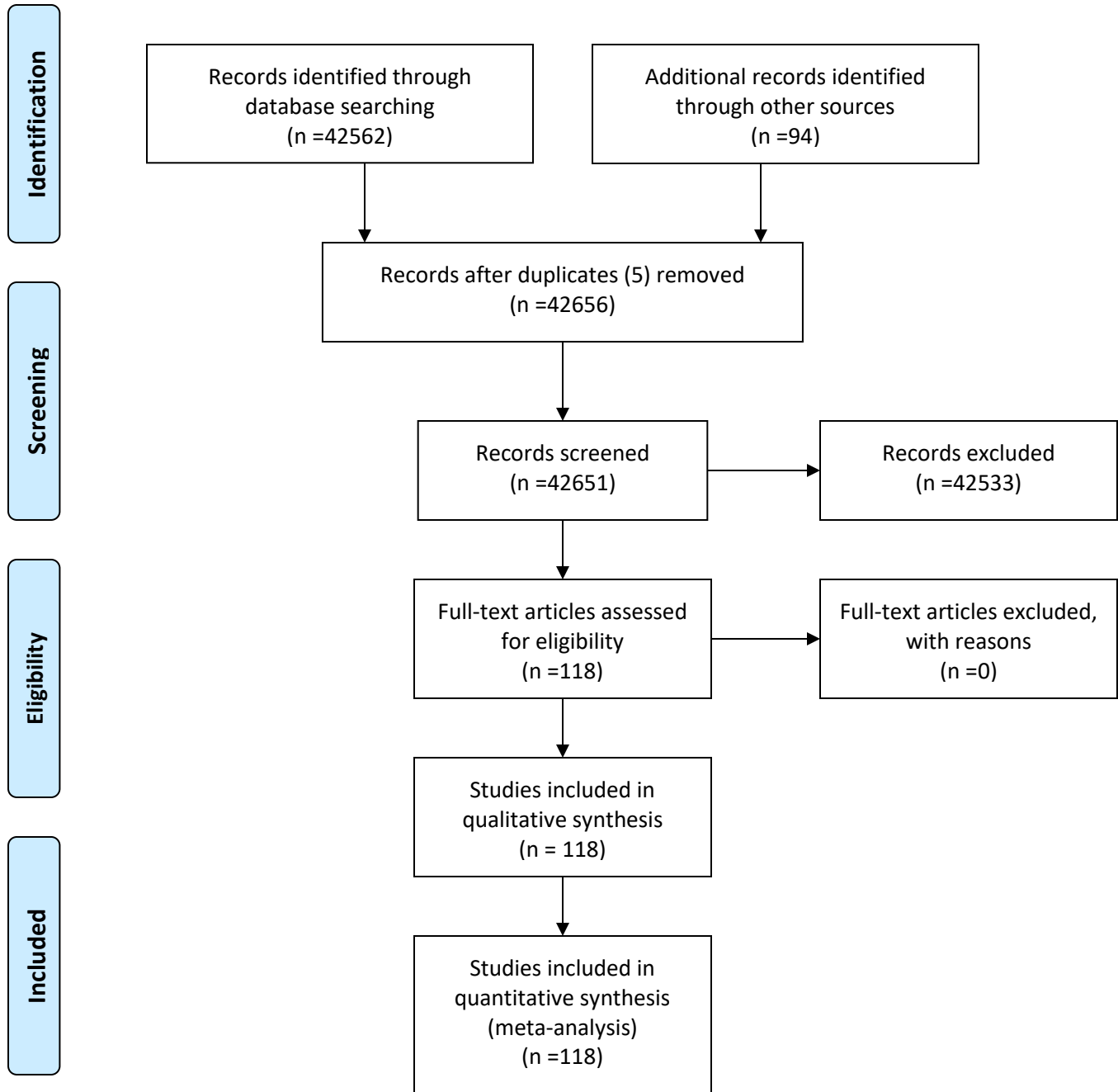
Fig 1. PRISMA diagram for the screening and selection of studies.

Fig 2. A schematic diagram of the SELEX procedures used to isolate oligonucleotide sequences specific to a desired molecular target from an entire DNA library

Fig 3. A labelled diagram depicting the sequence involved in the production of an aptamer-analyte-aptamer complex. (1) Analyte approaches the primary aptamer-electrode complex, (2) Analyte binds to the primary aptamer-electrode complex, (3) The secondary aptamer labelled with an ionised molecule approaches the electrode-primary aptamer- analyte structure, (4) The secondary aptamer binds to the analyte



PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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