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Tryptophan catabolism in epithelial ovarian carcinoma

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Abstract

Ovarian cancers are the most common cause of gynecological death, and the five-year survival rate for women diagnosed with epithelial ovarian carcinoma (EOC) remains extremely low at only 47%. Recent studies have highlighted the importance of the anti-tumor immune response in determining EOC clinical outcomes, and much research is currently being undertaken in an effort to reverse tumor immune evasion. One mechanism known to promote tumor immune evasion in multiple cancer types is tryptophan catabolism. Here we review the potential role of two rate-limiting enzymes that evolved separately to catabolize tryptophan, indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase 2 (TDO2), that may be active in ovarian cancers and result in the production of immune suppressive catabolites. Research to date has focused on IDO inhibitors, currently in clinical trials, but these therapies fail to inhibit TDO2. However, our mining of publically available data from clinical specimens suggest that TDO2 may also need to be targeted in ovarian cancer.

Keywords

epithelial ovarian carcinoma; tryptophan; TDO2; IDO1

Introduction

Ovarian cancers are the most common cause of death from gynecological disease in the United States. In 2019, it is estimated there will be 22,530 new cases of ovarian cancer and 13,980 deaths. High-grade serous ovarian carcinoma (HGSC), a subtype of epithelial ovarian carcinoma (EOC), accounts for around 70% of all ovarian adenocarcinomas and are most prevalent in postmenopausal women [1]. Women typically present with non-specific symptomatology such as abdominal distension, early satiety, and rarely with associated lymphadenopathy [1]. Thus, the vast majority of HGSCs present in either stage III with dissemination throughout the peritoneal cavity or stage IV with extensive lymph node

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CONFLICT OF INTEREST STATEMENT

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involvement [1]. Thus, the five-year survival rate for patients with advanced stage disease (III/IV) is remarkably low at 30%, with high rates of recurrent disease [1, 2].

Unlike most carcinomas, in EOC the main method of metastasis is through non-hematogenous spread. EOCs metastasize throughout the peritoneal cavity by direct seeding, in which cancer cells shed off the primary tumor into the peritoneal cavity [3]. Historically, EOC was thought to arise from the ovarian surface epithelium, but it is now accepted that it arises from the fallopian tube epithelium [1, 4]. Like other carcinomas, EOC can undergo an epithelial to mesenchymal transition (EMT) [5] that facilitates survival in anchorage-independent conditions [6, 7]. EOC cells shed from the fallopian tube and survive anchorage-independent conditions to attach to the ovary and multiple metastatic sites within the peritoneal cavity, making operative resection difficult and minimally effective [7–9]. Normal epithelial cells undergo apoptosis in response to being detached from the basement membrane and this specific type of cell death is termed ”anoikis” [10]. The ability of carcinoma cells to survive in suspension is defined as anoikis resistance [6, 7], and this contributes significantly to the metastatic potential of EOC [11]. Current treatment protocols involve initial debulking and staging surgery followed by systemic and/or intraperitoneal chemotherapy, typically with a combination of platinum- and taxane-based agents [6–9]. Unfortunately, EOC often recurs within 2 years of initial diagnosis as chemo-resistant disease, which contributes to a poor overall survival rate [12].

The exact mechanisms that facilitate direct seeding, survival during dissemination and peritoneal spread of EOC remain unclear and there is significant interest in understanding this process and developing agents to prevent or target metastatic EOC. The use and development of immunotherapy to promote anti-tumor immunity is expanding. In EOC, an increase in tumor-infiltrating T cells conveys a delayed time to recurrence [13], suggesting that immune stimulation through checkpoint inhibition should reduce EOC tumor burden. However, response rates to immune checkpoint inhibition (i.e., programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1)) in HGSC patients is only about 15% [14, 15], indicating a need to investigate additional mechanisms of EOC immune evasion. Suppression of cytotoxic T cells, significantly contributes to ovarian cancer progression [16, 17]. Immunosuppressive pathways such as tryptophan catabolism may contribute mechanistically to this process and play a critical role in determining clinical outcomes [18, 19]. This review presents rationale for investigating tryptophan catabolism in the context of EOC.

Tryptophan catabolism

Tryptophan is an essential amino acid that is ingested through the diet. In the cell, tryptophan can be used in several different ways, such as protein synthesis, production of serotonin, production of kynurenine or ultimately through the kynurenine pathway to generate nicotinamide adenine dinucleotide (NAD^+; Figure 1) [20]. There are three rate-limiting enzymes that can catabolize tryptophan into kynurenine: indoleamine 2,3-dioxygenase 1 (IDO1), indoleamine 2,3-dioxygenase 2 (IDO2), and tryptophan 2,3-dioxygenase 2 (TDO2) [20, 21].

IDO1 and IDO2 are highly expressed in the placenta, lung, and intestine. Under normal conditions minimal tryptophan is catabolized by these enzymes; however, they become highly active during immunological responses [21]. TDO2 is expressed in hepatocytes and is responsible for the majority of tryptophan catabolism under normal conditions [21]. The expression and function of TDO2 is regulated by a number of factors, including inflammatory stimuli [22], glucocorticoids [22, 23], heme-molecules [24], and via feedback inhibition by NADPH (nicotinamide adenine dinucleotide phosphate) [25]. Increased levels of tryptophan catabolism *via* the kynurenine pathway have been found in many human malignancies including, but not limited to, leukemia, glioma, lymphoma, breast cancer, hepatobiliary cancer and melanoma [26–30]. Additionally, the L-type amino acid transporter 1 (LAT1/*SLC7A5*), which transports large neutral amino acids, such as tryptophan, into cells, is overexpressed in many cancers including breast and ovarian clear cell carcinoma [31] and is associated with poor prognosis and chemo-resistance [32, 33].

Immune regulation by tryptophan catabolism

The immune system has multiple mechanisms for self-regulation, one of which is tolerance, which serves to dampen its response to infection and inflammatory insult in order to prevent over activation and the destruction of self tissues. This is also important during pregnancy to protect the fetus from the maternal immune system and tryptophan catabolism has been extensively studied in this context [34]. The kynurenine pathway has been shown to be an important player in this process of immune modulation [35]. Under normal conditions, T cells secrete IFNγ (interferon-gamma) which leads to upregulation of IDO1 in antigen-presenting cells (APCs). APCs are then able to catabolize local tryptophan, depleting it from the microenvironment to starve pathogens of tryptophan. In response to certain pathogens, such as *Chlamydia pneumoniae* and *Toxoplasma gondii*, the relative lack of tryptophan also leads to slowed CD4 T cell replication [36, 37]. Upregulation of IDO1 and TDO2 and increased levels of kynurenine metabolites have also been shown to suppress CD4 T cell proliferation and induce T cell death. This mechanism of T cell regulation has been proposed as a contributing factor to immune suppression in several disease states, including cancer [20, 21].

Metabolites of tryptophan catabolism act by both autocrine and paracrine mechanisms to promote tumorigenesis and tumor evasion from immune detection. Kynurenine acts in an autocrine fashion through the aryl hydrocarbon receptor (AhR) to provide anti-apoptotic signals that enhance survival under anchorage-independent conditions by upregulation of key genes that promote cell growth and survival [30, 38]. Through paracrine action, kynurenine can also suppress anti-tumor cytotoxic T cell function [30, 38]. Cultured human plasmacytoid dendritic cells (PDCs) exposed to inflammatory stimuli can induce class switching from CD4+ T cells to CD4+FOXP3+CD25+ regulatory T cells (Tregs) *via* upregulation of IDO [39], which then suppress the activity of cytotoxic T cells. The functionality of Tregs can be decreased by the IDO inhibitor (1-methyl-D-tryptophan), but is restored by the addition of kynurenine, suggesting that IDO is a critical factor in T cell regulation [39]. Furthermore, when T cells are exposed to IDO *in vitro*, CD4 and CD8 T cell proliferation is inhibited both by depletion of tryptophan and through kynurenine metabolite-mediated cell death [40, 41].

Role of IDO and TDO in cancer

Tryptophan catabolism and the kynurenine pathway have been highly studied in the field of oncology. Upregulation and increased activity of IDO1/2 or TDO2 have been found in a variety of cancers and are thought to have an important role in disease progression. Tumors that express IDO1/2 or TDO2 can suppress and evade the anti-tumor immune response [30, 40, 42]. Tumor cells that express IDO have fewer tumor-infiltrating lymphocytes (TILs), indicating that tryptophan catabolism can aid tumors in immune evasion [43].

The kynurenine pathway plays a role in progression of many tumors types, such as human meningioma, where IDO is highly expressed and the tryptophan metabolites 5-hydroxy indole acetic acid (5-HIAA) and kynurenine are increased [44]. In triple negative breast cancer (TNBC), TDO2 protein levels increased rapidly during conditions of anchorage-independent survival and are also increased by inflammatory activators of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) [38]. *TDO2* is a direct target of the microRNA-200c (miR-200c) in more indolent breast cancer subtypes, but continues to be expressed in TNBC due to their loss of miR-200c [45].

An important measure of tryptophan metabolisms that has been indicated in prognostication of different cancers is the kynurenine-to-tryptophan ratio (KTR), which when elevated indicates that tryptophan is being metabolized through the kynurenine pathway by IDO1/2 or TDO2. For example, clear cell renal carcinoma patients with a higher KTR have lower survival rates indicating that tryptophan catabolism is an important prognostic indicator [46]. Likewise, increased KTR was also found to be associated with increased squamous cell lung cancer risk [47]. Our study in presurgical plasma samples from patients with breast cancer versus healthy patients did find that tryptophan was significantly lower in the plasma of breast cancer patients with estrogen receptor alpha-negative tumors than normal donors; however contrary to expected results, kynurenine was also lower in the cancer patient plasma compared to cancer-free controls [31]. Although we predicted, based on prior studies from other types of cancer including breast [28], that tryptophan would be lower and kynurenine higher in breast cancer patients, our study had a low percentage of patients with advanced stage disease, where KTR might be expected to be higher due to increased disease burden. Additionally, we had a relatively young patient cohort than is typical for most breast cancer studies. Kynurenine production by tumor cells may not be enough to result in increased plasma levels of circulating kynurenine and the kidneys are efficient in catabolizing kynurenine [31].

IDO and TDO in ovarian cancer

IDO1/2 have been studied in EOC and it has been postulated that they could serve as effective therapeutic targets for this disease [17, 19]. In advanced EOC, the presence of intratumoral TILs correlates with improved clinical outcomes [13]. In fact, 56% of surgically resected EOCs sampled have high IDO expression that correlates with decreased levels of CD8+ T cells [19]. Interestingly, increased levels of IDO are further positively correlated with impaired survival in patients with serous type ovarian cancer [18]. Gene expression profiles of HGSC cells show that *IDO* positively correlates with chemo-

resistance, reduced survival, and poor prognosis [48]. Indeed, IDO upregulation promoted peritoneal metastasis of ovarian cancer by creating an immunosuppressive environment within the peritoneal cavity [49].

Several clinical studies involving IDO inhibition in ovarian cancer are ongoing (Table 1). One trial is investigating genetic polymorphisms within IDO and how they affect the outcome of EOC patients [50]. Other studies are investigating presurgical treatment with IDO1 inhibition using Epacadostat (an IDO1-specific inhibitor) in combination with other agents in stage III-IV EOC to determine if this treatment stops the growth of tumor cells. In particular, one study, , is testing Epacadostat to treat patients with platinum-resistant ovarian, fallopian tube, or peritoneal cancers, while another, , is investigating the effectiveness of the combination of Epacadostate with anti-PD-1 immunotherapy.

TDO2 has been less well-studied in ovarian cancer. A study by Hsu *et al.* in 2012 looking at IκB kinases (IKKs) and their role in ovarian cancer invasion and metastasis showed that TDO2 is expressed in ovarian cancer cell lines. This study examined how IKK inhibitors affect gene expression and found that in addition to expected changes in genes involved in cellular motility and inflammation, *TDO2* and another enzyme in the kynurenine pathway, kynureninase (*KYNU*), appear to play a role in IKK signaling [51], though the authors did not further investigate the role of trypophan catabolism in this process [51]. Gene expression similarities between EOC and TNBC [52] prompted us to examine whether *TDO2* or *IDO* were more well correlated with tumor progression and outcome in EOC, since in breast cancer we found that *TDO2* was correlated with clinical parameters, while *IDO1* was not [31]. In the Tothill ovarian cohort (n = 293, [53]) we examined correlations between *TDO2* and *IDO1* and ovarian cancer outcomes. We found that while *TDO2* was significantly associated with disease stage, recurrence and survival in ovarian cancer, *IDO1* was not (Figure 2). These data indicate that TDO2 may be an important potential target in ovarian cancer and provides a rationale for further investigation into testing drugs that target TDO2 or dual inhibition of both TDO2 and IDO in EOC.

Conclusion

Ovarian cancers are the most common cause of gynecological death. Unfortunately, EOC treatment is also extremely difficult since chemo-resistance often develops rapidly. The tryptophan catabolism pathway is well known to play a role in the aggressive nature of cancer. Higher levels of IDO1 and IDO2 and decreased TILs have been reported in more aggressive late-stage EOC compared to early stage EOC. TDO2, on the other hand, has not been examined in EOC. Gene expression data from clinical specimens suggests that *TDO2* correlates with disease progression and may be a relevant target in the treatment of EOC. Thus, further exploration into the role of TDO2 in serous ovarian carcinoma is warranted.

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ABBREVIATIONS:

5-HIAA	5-hydroxy indole acetic acid
AhR	aryl hydrocarbon receptor
APCs	antigen presenting cells
EMT	epithelial to mesenchymal transition
EOC	epithelial ovarian carcinoma
HGSC	high grade serous ovarian carcinoma
KYNU	kynureninase
IHC	immunohistochemistry
IDO	indoleamine 2,3-dioxygenase
IKKs	IκB kinases
KTR	kynurenine-to-tryptophan ratio
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NFkB	nuclear factor kappa-light-chain-enhancer of activated B cells)
PD-1	programmed death protein 1
PDCs	plasmacytoid dendritic cells
PD-L1	programmed death-ligand 1
TILs	tumor infiltrating lymphocytes
TDO2	tryptophan 2,3-dioxygenase 2
TNBC	triple-negative breast cancer
Tregs	regulatory T cells

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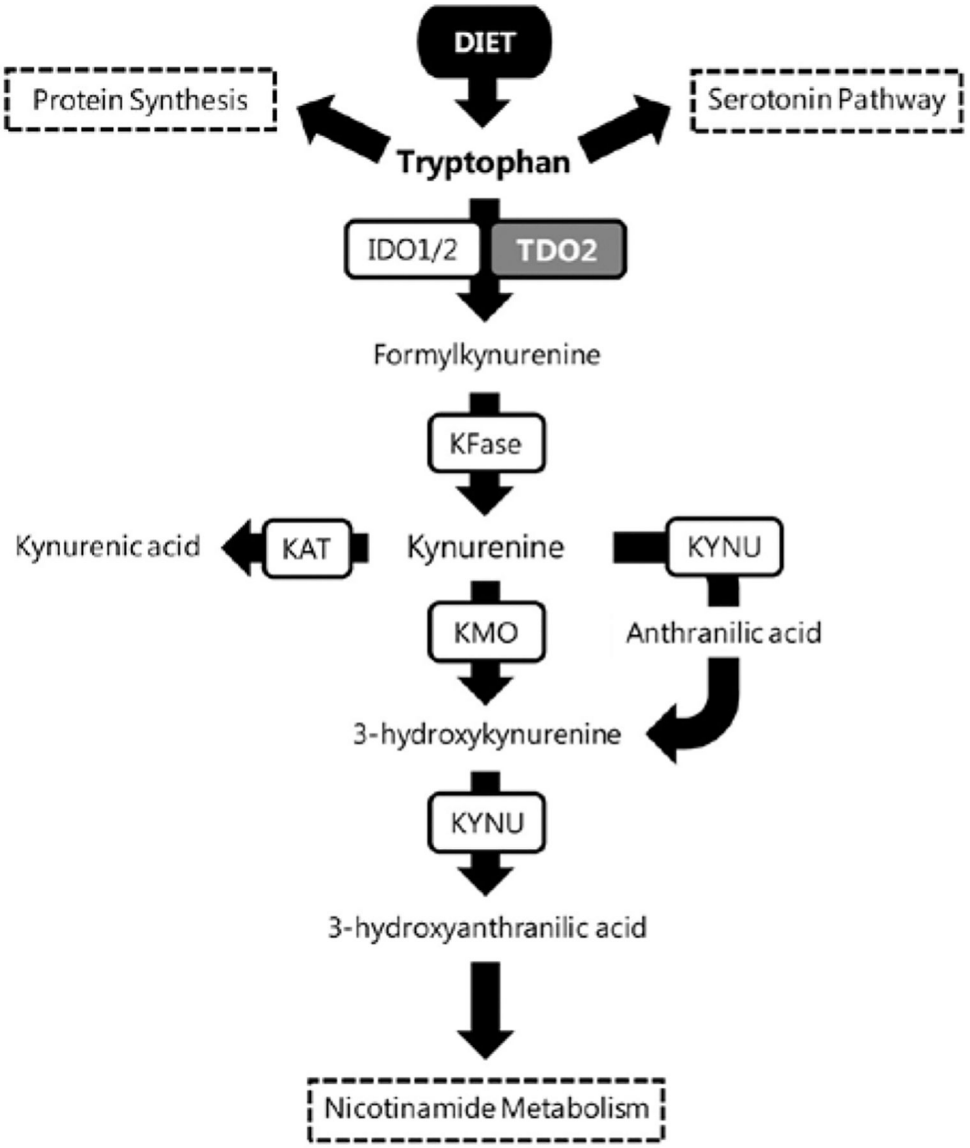

Figure 1.

The tryptophan catabolism pathway. The essential amino acid tryptophan is catabolized through three pathways: protein synthesis, the serotonin pathway and nicotinamide metabolism. IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; KFase (also known as AFMID), arylformamidase; KAT (AADAT), kynurenine aminotransferase; KYNU, kynureninase; KMO (K3H), kynurenine 3-hydroxylase.

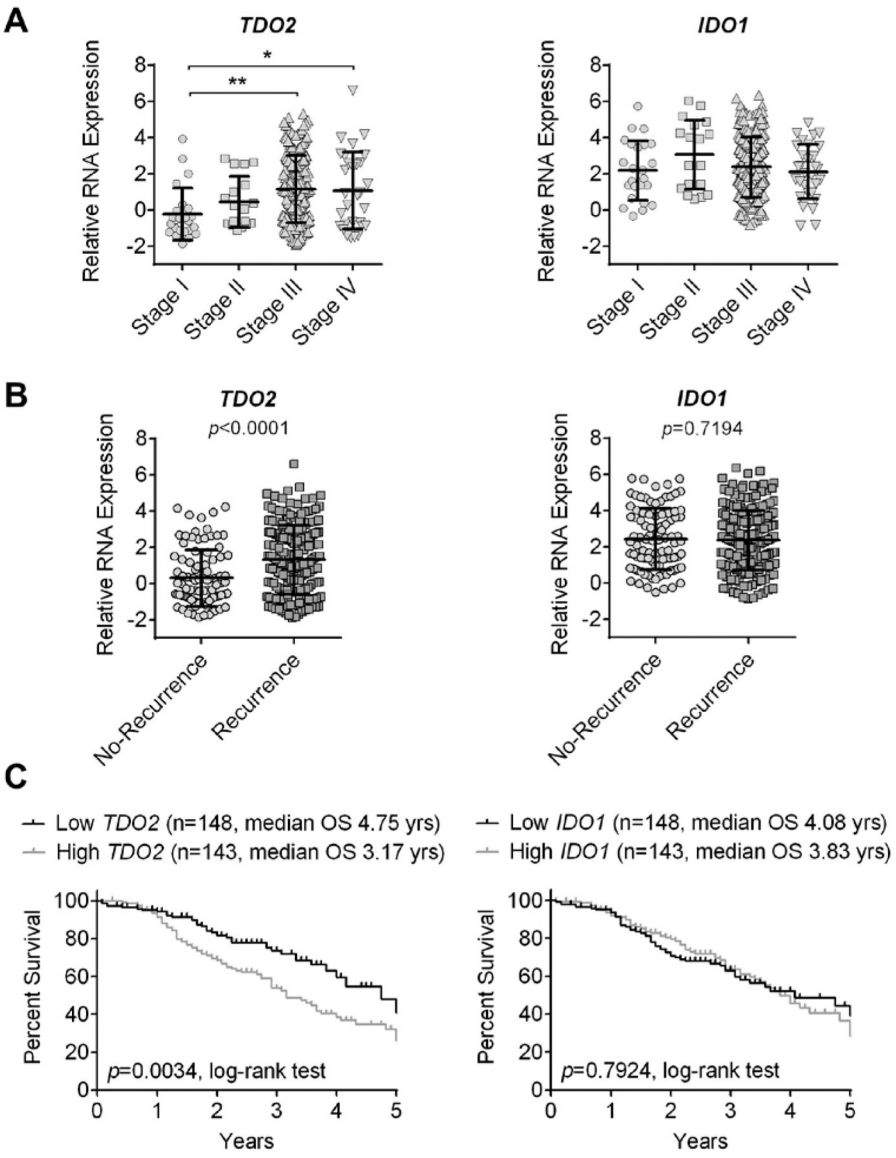

Figure 2.

TDO2 and *IDO1* levels in ovarian cancer patients from the Tothill cohort (n = 293). RNA expression was compared between **(A)** disease stage, **(B)** recurrence status, and **(C)** the five-year survival rate of patients with high versus low levels of expression based on the median. Comparisons were statistically analyzed using one-way ANOVA for disease stage (*TDO2* $p = 0.003$, *IDO1* $p = 0.262$), unpaired t-test for recurrence, and log-rank for survival; mean ± standard deviation, * $p < 0.05$, ** $p < 0.01$.

Table 1.

Clinical research on IDO-targeted therapies in ovarian cancer.

Trial name	NCT #	Study synopsis
How our immune system can help fight cancer		Tregs are immunosuppressive and promote cancer progression by inhibiting the anti-tumor immune response. In most T cell populations tryptophan depletion leads to decreased activity and viability, but Tregs are less susceptible to tryptophan depletion than other T cell populations. We hypothesize that genetic polymorphisms within IDO alter enzymatic activity within Treg populations and affect patient outcomes. This study will examine IDO polymorphisms in EOC tumors and ascites.
Epacadostat before surgery in treating patients with newly diagnosed stage III-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer		Epacadostat is an IDO1 inhibitor that may reduce tumor cell growth. This study will examine how neoadjuvant treatment with epacadostat affects disease progression (and adverse reactions) in newly diagnosed stage III-IV epithelial ovarian, fallopian tube or primary peritoneal cancers.
DEC-205/NY-ESO-1 fusion protein CDX-1401, poly ICLC, and IDO1 inhibitor INCB024360 in treating patients with ovarian, fallopian tube, or primary peritoneal cancer in remission		Antigens, such as the cancer-specific antigen NY-ESO-1 protein, are found on many cancer cells and assist the immune system in targeting and destroying cancer cells. Some tumors, however, express IDO which promotes tumor growth and progression by suppressing the immune system. This study will determine the side effects, best dose and initial effectiveness of combining the IDO inhibitor INCB024360 with a cancer vaccine (DEC-205/NY-ESO-1 fusion protein CDX-1401) and an immune stimulant (poly ICLC). The goal is to generate a stronger, longer lasting anti-tumor immune response in patients with ovarian, fallopian tube and primary peritoneal cancers in remission.
Study of DPX-Survivac vaccine therapy and epacadostat in patients with recurrent ovarian cancer		This study will determine the safety and immunomodulatory effects of combining the IDO1 inhibitor epacadostat with the immunotherapeutic vaccine DPX-Survivac and cyclophosphamide chemotherapy in patients with recurrent ovarian, fallopian tube or peritoneal cancers.
A phase 2 study of the IDO inhibitor INCB024360 versus tamoxifen for subjects with biochemical-recurrent-only EOC, PPC or FTC following complete remission with first-line chemotherapy		This randomized study will examine the effectiveness of the IDO inhibitor INCB024360 compared to tamoxifen in biochemical recurrent ovarian cancer patients following complete remission with first-line chemotherapy.
Intraperitoneal natural killer cells and INCB024360 for recurrent ovarian, fallopian tube, and primary peritoneal cancer		This study will determine the maximum tolerated dose of the IDO inhibitor INCB024360 when administered as part of a larger regimen of haploidentical donor NK cells and IL-2 following a non-myeloablative cyclophosphamide/fludarabine chemotherapy regimen in recurrent ovarian, fallopian tube and primary peritoneal cancers.
Safety and efficacy of CRS-207 with epacadostat in platinum-resistant ovarian, fallopian or peritoneal cancer (SEASCAPE)		This study will determine the safety and potential efficacy of the investigational cancer drugs CRS-207 (an immune stimulant), epacadostat (an IDO1 inhibitor) and pembrolizumab (anti-PD-1 immunotherapy) in patients with platinum-resistant ovarian, fallopian tube or peritoneal cancers.
Pembrolizumab and epacadostat treating participants with recurrent, persistent or progressive ovarian clear cell carcinoma		This phase II trial will determine the effectiveness of the combination of pembrolizumab and epocadostat in treating patients with ovarian clear cell carcinoma.

EOC, epithelial ovarian carcinoma; FTC, fallopian tube cancer; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; NK, natural killer; PD-1, programmed cell death protein-1; PPC, primary peritoneal cancer; Tregs, regulatory CD4 T cells.