***Review Article***

# Urokinase Plasminogen Activator Receptor (uPAR) Targeted Therapy with Switchable Chimeric Antigen Receptor T-Cell (sCAR T-Cell) Potential as Pancreatic Cancer Immunotherapy Agent

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**Abstract**

Pancreatic cancer is the cancer with highest mortality-incidence rate compared with other types of cancer. Most cases can only be treated palliatively. Targeted therapy comes as an alternative to its treatment especially with Switchable CAR T-cells (sCAR T-cells). In pancreatic cancer, urokinase plasminogen activator receptor (uPAR) is a specific target that is excessively expressed in tumor cell microenvironment. Targeted therapy using sCAR T-cells has been proved safe and effective in other types of malignancy such as B cell lymphoma, so it has potency as immunotherapy agent in pancreatic cancer patient.

**Keywords:** Pancreatic cancer, Immunotherapy, sCAR T-cells, uPAR

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## Introduction

Cancer is the largest contributor to morbidity and mortality worldwide. According to the Global Burden of Cancer Study (GLOBOCAN) report released in September 2018, there are 18.1 million new cases and 9.6 million deaths from all forms of cancer worldwide. Treatment of cancer is very expensive and costs more than US$ 150 billion globally.[1,2]

In South East Asia, cancer is the leading cause of death, causing more than 1.3 million deaths annually.[3] High mortality rates are correlated with late diagnosis, so treatment has started at advanced disease stages, particularly in South East Asia, where 50 percent of cases have lately been diagnosed. Otherwise, massive treatment at the later stage of the disease care is very costly, resulting in a very remarkably financial burden on 77 percent of patients.[4]Indonesia has the largest proportion of cancer patients in South East Asia, with more than one million cases.[5] One of the most debilitating cancers is pancreatic cancer.

Pancreatic cancer is the 12th most common cancer in the world. Although it is considered low in prevalence, the main concern for pancreatic cancer is due to its high mortality rate, which is approximately 94 percent, higher than any other type of cancer.[6] Pancreatic cancer is also responsible for the fourth most common cancer-related deaths and is expected to be second-tier by 2030.[7] High mortality rates are supported by an inadequate detection system, according to the finding that only 7% of cases are detected at an early stage, leading to difficult treatment and many adverse outcomes.[8]

The modality of pancreatic cancer therapy depends on the stage of disease. According to earlier data, due to a high rate of detection in advanced phases, resectable cases encompass only 10% of the case fraction, while adjuvant therapy (chemotherapy and radiotherapy) must be performed on 30% of the patients and, unfortunately, 60% of the patients can only be palliatively treated.[9] Not only that, recurrence risk in the surgical procedure (though followed by adjuvant therapy) is high (80 %) due to incomplete resection, neuronal, and

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vascular invasion, which leads to death following the intervention.[10,11] Due to that scenario, new alternatives such as targeted therapy is favorable to be applicated for pancreatic cancer treatment.

Targeted therapy is a treatment procedure that is based on findings in molecular biology and genetics, related to the nucleotide mutations of the malignant cell.[12] It is related to the interaction of certain drugs or molecules with a particular target in the cancer cell, resulting in cell death.[13] Genetically engineered immune cell, Chimeric Antigen Receptor (CAR) T-cell is the example of this future treatment.[14] The use of this modality in pancreatic cancer has been evaluated on some targets, including Cluster of Differentiation (CD)-24, Carcinoembryonic Antigen (CEA), Mucin-1, Prostate stem cell antigen (PSCA), Mesothelin, Fibroblast activation protein (FAP), and Human epidermal growth factor receptor 2 (Her-2). Preclinical and early phase clinical trials have shown a positive outcome of the CAR T-cell application for pancreatic cancer.[15,16] However, there are some safety and toxicity concern related to CAR T-cell use.

CAR T-cell use is associated with some serious adverse event.[17] Adverse event associated with CAR T-cell is thought to arise from excessive immune cell stimulation in the form of Cytokine Release Syndrome (CRS), Macrophage Activation Syndrome (MAS), Hemophagocytic Lymphohistiocytosis (HLH) and neurotoxicity (cerebral edema).[18,19] CRS is the most significant reaction interlinked to the death of a patient in a treatment session.[20]

Based on the toxicity issues, we need further targeted therapy to enhance the protection and specificity profile of pancreatic cancer treatment. Switchable CAR T-cells is an alternative due to better management that can be used to control T-cell activity without killing the cell itself and also provides time for the cell to rest and recover which is an important component in the conservation of the capacity and prevention of the CRS phenomenon.[21] In addition, the use of more specific cell surface receptors in pancreatic cancer, Urokinase Plasminogen-activator Receptor (uPAR) could contribute to a better outcome of treatment.[22]

Our study focuses on the use of Switchable CAR T-cell targeting a particular molecule, Urokinase Plasminogen-activator Receptor (uPAR) for pancreatic cancer treatment, which is supposed to result in improved treatment response.

**Role of uPAR in pancreatic cancer**

Urokinase plasminogen activator (UPA) is a serin protease that regulate various pathways related to tumor development, cell motility, matrix degradation,metastatic process, and angiogenesis.[23–25] The role of UPA started by the binding to its receptor (uPAR) that is located on the plasma membrane by the Glycosylphosphatidylinositol (GPI) component that causes conversion of plasminogen to plasmin. Plasmin is a potent extracellular matrix degrading enzyme capable of stimulating the matrix metalloproteinase to digest the surrounding connective tissues, which is responsible for promoting migration and local infiltration of tumor cells and endothelial cells in the metastatic cascade.[26,27] In malignant conditions, especially pancreatic cancer, the uPA receptor is expressed excessively, particularly in invasive cells and various stromal cells in the tumor microenvironment, including endothelial tumor angiogenic cells, active macrophages, and active fibroblasts.[28]

Pancreatic cancer is a type of cancer characterized by extensive tumor stroma, which includes 50-85 percent of the mass of the tumor. Pancreatic cancer is characterized by a high expression of the uPAR element, which can be found in approximately 80-98 percent of pancreatic cancer tissues and 58 percent of pancreatic cancer tissues have an amplification of the uPAR genes..[29] Overgrowing uPAR is also associated with poor prognosis in pancreatic cancer patients.[30]

UPAR is the best biomarker in terms of distinguishing pancreatic cancer cells than normal cells (best of 15 marker) nor chronic pancreatitis (best of 29 marker).[31] It is supported by the fact that this receptor is not expressed in normal pancreas and chronic pancreatitis, so it is very likely to be included in targeted therapy.[31,32]

Targeting UPAR has the potential to increase the retention of nanoparticles in tumor cells, as well as to increase the efficacy of drug delivery and cell distribution through receptor-related internalization. The suppression of uPA and uPAR activity may slow the proliferation of pancreatic tumors in the animal model.[33] Down-regulation of uPA expressions may weaken the phenotype of stem cell[34], suppress the formation of pancreatosphere[35], and restore sensitivity to gemcitabine. On the other hand, over expression of uPA tends to increase drug resistance and pancreatosphere formation by cultured pancreatic cancer cells and promotes

tumor growth in vivo.[35] UPA can also inhibits miR-124 expression via a negative feedback loop that increases Lhx2 expression, contributing to pancreatic cancer stem cells. UPA can also interact with stromal cells that activate LHX2 and enhance stemness via paracrine signaling. UPA-mediated paracrine modulation may be one of the reasons for the difficulties of treatment with traditional chemotherapy in uPA over-expressed tumors.[36]

UPA can bind directly to various transcription factors, such as HOXA5, which performs p53 expression up-regulation thru direct p53 promoter transactivation.[37] Inhibition of HOXA5 binding to its DNA sequences by uPA, restricting the ability of HOXA5 to activate the p53 promoter, and restricting p53 expression in pancreatic cancer cells..[35]

**Design of CAR T-cell Structure**

Chimeric antigen receptor (CAR) is a genetically modified receptor that can be inserted into a cell. The application of this component can be found on the T cell effector (CAR T-cell). There are three domains on CAR as follows: ectodomain, transmembrane domain and endodomain. Ectodomain in CAR T-cell has a single-chain fragment variant (scFv) that plays a role in the identification of extracellular antigens. Otherwise, the CD28 transmembrane domain helps to ensure the integrity of the CAR expression and the endodomain that has two functions as co-stimulator (CD28, 4-1BB or OX40) and signal activator (CD3). This domain induces T-cell activation, proliferation, and cytokine secretion to kill tumor cells.[38,39]

Sequentially, CAR T-cell processes are: (i) removal of mononuclear cells from peripheral blood; (ii) separation of T-cells from mononuclear cells using immunoselective beads that are activated using anti-CD3 and then activated by anti-CD3 and IL2; (iii) alteration of CAR T cell genetics; (iv) in vitro expansion of T-cells by lentiviral vector; (v) evaluation of CAR T-cells; (vi) injection of CAR T cell to the patient.[40]

**CAR T cell mechanism of actions**

There are three steps of CAR T cell in tumor cells elimination. First, recognition of CAR T through its ectodomain after injected to human body. There is no need of major histocompatibility complex (MHC) for this recognition so that increases the potency of artificial T cell in immunotherapy.[41] This mechanism contributes to the propagation of the signal across the cell membrane to the endomain. Second, two types of signal are produced by the endodomain receptor, the activator (CD3 domain) and the co-stimulatory signal (CD28,4-1BB or OX40 domain). These contribute to the activation of the CAR T cell. Third, activated CAR T cells release cytokines and transcription factors, such as Fas Ligand (FasL), tumor necrosis factor-related ligand-inducing apoptosis (TRAIL) and interferon (IFN)-gamma, which induces cytotoxic activity against tumor cells. This process enhances the efficiency and resilience of the CAR T cell by means of an IL-2 secretion mechanism.[42] Illustration of this mechanism is depicted on figure 1.

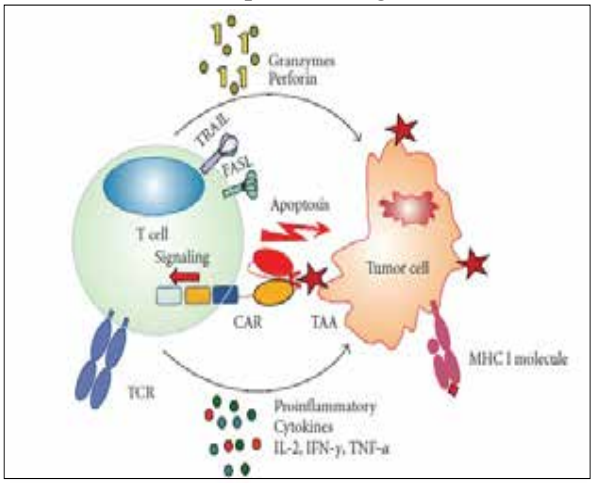


**Figure 1**. Target Cell Elimination by CAR T cell.[42]

The CAR T cell immunotherapy method has shown promising results in a variety of hematological malignancies and solid tumors.[43] However, toxicity hazards such as cytokine release syndrome (CRS) and "on-target, off-tumor" process induced toxicity can be fatal. This may be due to the inability to control T cells and the lack of a particular tumor cell antigen. In fact, the same antigens were typically expressed in healthy tissues.[44,45] Therefore, in order to increase the security of the application of CAR T cells, a method is required to regulate the behavior of the CAR cell. This is called the Switchable CAR T cell (sCAR T cell), which is a redesign of the CAR T cell.[46]

***sCAR T Cell Mechanism of Action***

Unlike the CAR T cell, in the identification of tumor cell antigens, the sCAR T cell relies on its switch component.[47] The component is a peptide neo-epitope – antibody fragment (PNE-Fab) complex. Peptide neo-epitope was derived from GCN4 transcription factor and then presented to antibody fragrances (Fab) to a specific antibody position.[48] The Fab was derived from anti-uPAR antibody (VIM5) which selectively bind to uPAR (Figure 2).

**sCAR T Cell Mechanism of Action**

Differ from CAR T cell, in recognizing tumor cell antigens, sCAR T cell depend on its switch component.[47] The component is a peptide neo-epitope–antibody fragment (PNE-Fab) complex. Peptide neo-epitope was derived from a GCN4 transcription factor and added to a particular location (Fab).[48] Fab was derived from anti-uPAR antibody (VIM5) that selectively binds to uPAR (Figure 2).

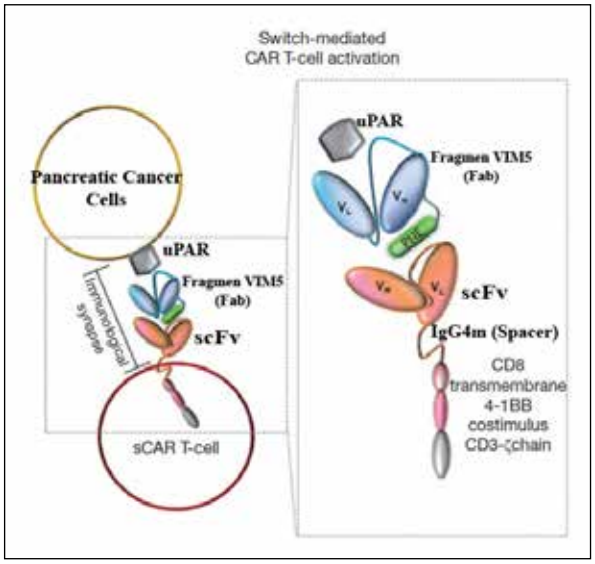


**Figure 2.** Schematic design of sCAR T cell targeting uPAR in pancreatic cancer therapy.

The switchable CAR (sCAR) portion was derived from the scFv region of the 52SR4 antibody that selectively targets the PNE. This scFv region was then integrated into the second generation of the CAR T cell, which has co-stimulatory 4-1BB (CD137) on its endomain and spacer in the form of IgG4m on its ectodomain. IgG4m spacer was chosen because it has a shorter structure than other spacers, such as CD8 and IgG4, so that it has the best sCAR T cell operation.[43,47]

This mechanism of action has been shown in a study performed by Rodgers et al. on the clinical use of sCARs for CD19-targeted B cell malignancy. Based on the study, sCAR T cells could eliminate tumor cells if only a switch Fab in the form of a light chain N terminus (LCNT) was present (Figure 3).[47]

The advantage of this switchable approach is that it can reduce the risk of serious toxicity by encouraging multistep titration in order to achieve optimal therapeutic levels by controlling the molecular concentration and can be a selective T cell activation regulator either by adding or reducing the small molecule (switch component).[49]

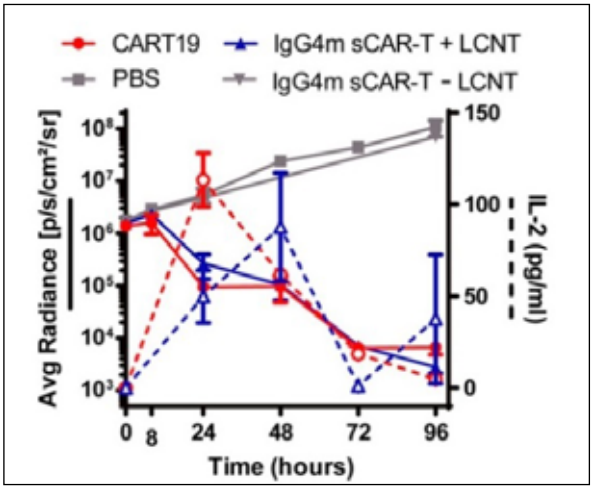


**Figure 3**. Differences between CART19 and sCART19. sCART19 acted only if there was Fab in the form of LCNT, whereas CART19 was not depended on LCNT. The tumor cells growth was represented by average (Avg) Radiance.[47]

**Opportunities for Application of uPAR Targeted Therapy sCAR T Cell in Pancreatic Cancer Therapy**

The use of uPAR-targeted sCAR T cells in pancreatic cancer therapy has great potential. A research performed by Warheit et al. used cisplatin-based amino terminal fragment-PEGylated-Iron oxide nanoparticle (ATF-PEG-INP) and uPAR-targeted doxorubicin in pancreatic cancer therapy. The ATF acted as a ligand targeting uPAR. The study showed that ATF-PEG-IONP-Cis had a more inhibitory effect on pancreatic cancer proliferation than cisplatin lacking ATF-PEG-IONP, as shown by the restriction of the CD31 cell marker (angiogenesis marker) and ki67 (tumor cell proliferation marker) compared to traditional chemotherapy using cisplatin (Figure 4) or doxorubicin only (Figure 5).[49]

While IONP use in pancreatic cancer treatment has shown promising efficacy, exposure to this nanoparticle leads to several adverse health effects. IONP toxicity causes massive inflammation and higher pulmonary fibrosis relative to higher particle consumption at equal doses.[50] IONP also related with neurodegenerative disease, including Parkinson disease.[51] Adverse IONP event is thought to occur by many pathways such as iron accumulation, protein aggregation, and oxidative stress.[52] Reflecting the severity of the harmful impact caused by IONP, sCAR T-cell is a promising option for pancreatic cancer treatment with a better safety profile.

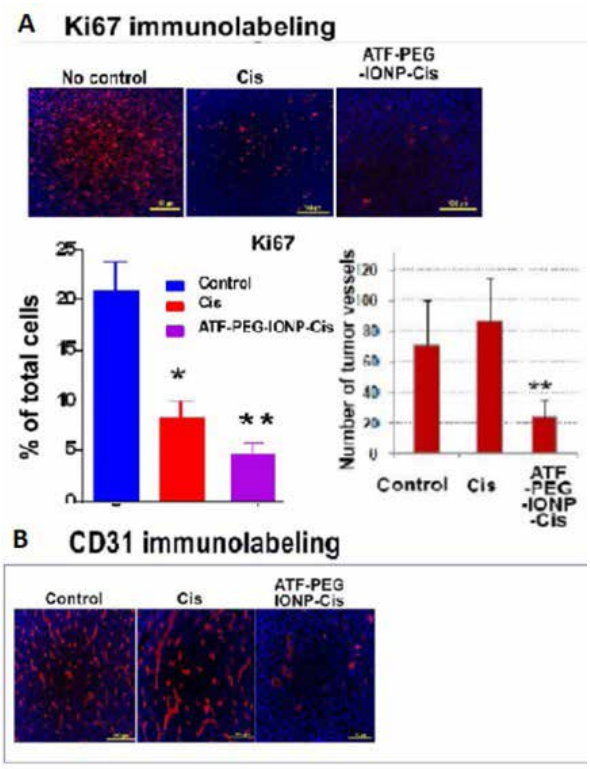


**Figure 4.** Inhibition to proliferation and angiogenesis of pancreatic cancer by ATF-PEG-IONP-Dox is better than Cisplatin.[49]

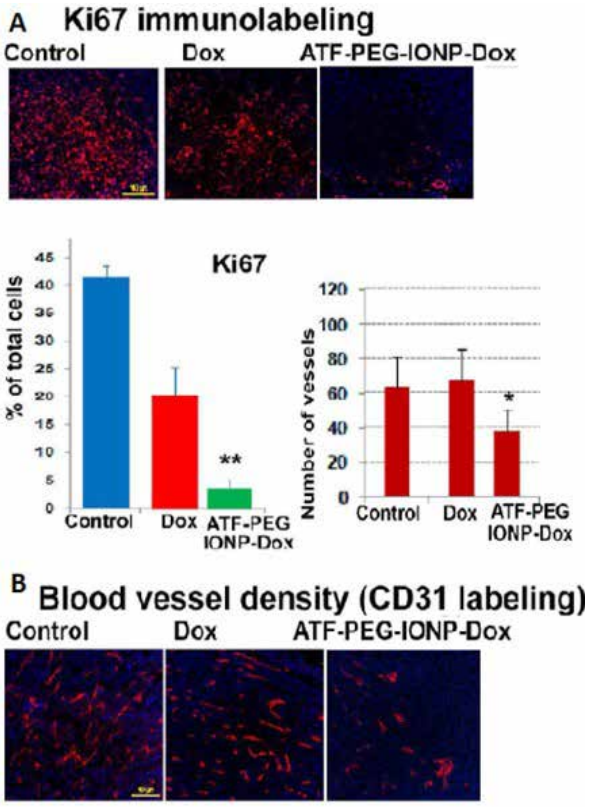


**Figure 5.** Inhibition to proliferation and angiogenesis of pancreatic cancer by ATF-PEG-IONP-Dox is better than Doxorubicin.[49]

## Conclusion

uPAR targeted therapy with sCAR T-cell is potential to be used in pancreatic cancer treatment. uPAR is the most specific pancreatic cancer biomarker, meanwhile sCAR T-cell use facilitating graded titration and better T cell regulation which is used to prevent adverse outcome of pancreatic cancer treatment, including Cytokine Release Syndrome.

## Recommendations

Future research is needed to determine most functional parts of VIM5 antibody fragment that can be inserted to PNE that can optimizing sCAR T cell work. Effect analysis, dose, and side effects must be assessed in next research for maintaining uPAR targeted therapy with sCAR T-Cell effectiveness and safety.

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None

## Conflict of Interest

Authors declared no conflict of interest

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