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Pankreas Kanserinin Erken Evrelerde Teşhisi için Yapılan Biyosensör Çalışmaları

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Öz

Pankreas kanseri, kötü prognoza ve yüksek ölüm oranına sahip bir kanser türüdür. Agresif bir kanser türü olan pankreas kanserinin erken tespit edilmesi oldukça zordur ve genellikle ileriki evrelerde kesin olarak teşhis koyulmaktadır. Teşhis konulan hastalarda 5 yıllık sağkalım oranı ortalama % 6'dır. Bu yüzden, pankreas kanserinin erken teşhis edilmesi, erken müdahale sonucu sağkalım oranını arttırmada ve ölüm oranlarını azaltmada önemli bir role sahiptir. Pankreas kanserinin teşhis edilmesinde geleneksel yöntemler olarak biyopsi, ultrason, manyetik rezonans gibi görüntüleme teknikleri kullanılır ancak bu teknikler pahalı, çok zaman almakta ve doğru, kesin sonuçlar alabilmek için alanında uzman kişiler tarafından yapılması ve analiz edilmesi gerekmektedir. Bu nedenle daha kolay ulaşılabilen, ucuz, herkes tarafından kullanılabilme özelliğine sahip ve doğru sonuç verme olasılığı yüksek araçlar olan biyosensörler, pankreas kanserinin teşhisinde kullanılması önerilmiştir. Bu çalışmada pankreas kanserinin varlığında açığa çıkan miRNA, protein gibi biyobelirteçlerin tespitine yönelik biyosensör çalışmalarına yer verilmiştir.

Anahtar Kelimeler
Pankreas Kanseri; Pankreas Kanseri Belirtileri; Biyobelirteçler; Biyosensörler.

Biosensor Studies For The Diagnosis Of Pancreas Cancer In Early Stages

Abstract

Pancreatic cancer is a type of cancer with a poor prognosis and high mortality rate. Pancreatic cancer, which is an aggressive type of cancer, is very difficult to detect early and is usually diagnosed in later stages. The 5-year survival rate in diagnosed patients is 6% on average. Therefore, early detection of pancreatic cancer has an important role in increasing the survival rate and reducing mortality rates as a result of early intervention. Imaging techniques such as biopsy, ultrasound, and magnetic resonance are used as traditional methods in the diagnosis of pancreatic cancer, but these techniques are expensive, take a lot of time and need to be performed and analyzed by experts in the field in order to obtain accurate and precise results. For this reason, biosensors, which are more accessible, inexpensive, can be used by everyone, and have a high probability of giving accurate results, have been suggested to be used in the diagnosis of pancreatic cancer. In this study, biosensor studies for the detection of biomarkers such as miRNA and protein, which are revealed in the presence of pancreatic cancer, are included.

Keywords
Pancreatic Cancer; Pancreatic Cancer Symptoms; Biomarkers; Biosensors.

1. Introduction

Pancreatic cancer (PC) is a type of cancer that depends on genetic and environmental conditions (Abe et al. 2021). The risk of developing pancreatic cancer in individuals with a first-degree relative with pancreatic cancer [9.0 (95% CI, 4.5-16.1)] is higher than in individuals without a family history of pancreatic cancer [2.4 (95% CI, 0.06-13.5)] (Klein et al. 2004). Smoking is the biggest environmental factor that causes pancreatic cancer (Rulyak et al. 2003). Pancreatic cancer is a fatal disease involving highly aggressive pancreatic ductal adenocarcinoma (PDAC), accounting for 85-95% of all pancreatic malignancies, with a 5- year survival rate of 1.2-6% (Conroy et al. 2016). PDAC is a heterogeneous type of cancer that includes endocrine and exocrine pancreatic cancers and accounts for more than 90% of all pancreatic tumors (Quian et al. 2019). PDAC does not arise directly; however, it is known to arise from non-invasive precursor lesions that undergo histological and genetic progression resulting in invasive neoplasia. The most common premalignant precursors of PDAC are pancreatic intraepithelial neoplasms (PaINs) (Previdi et al. 2016). Early detection of pancreatic cancer is extremely difficult, and most patients are not detected until the disease has spread (Foley et al. 2016). The most common symptoms of pancreatic cancer are pain, jaundice, and weight loss. Jaundice is caused by a disproportionate increase in bilirubin and alkaline phosphatase levels in the blood as a result of obstruction of the gallbladder due to tumor shown in Table 1 and table 2 (Freelove et al. 2006). The color of the urine is dark due to the high level of conjugated bilirubin and the absence of urobilinogen, while the color of the stool is pale due to the lack of stercobilinogen. Severe itching, which causes jaundice, may also occur with increased bilirubin levels. As observed in pancreatic cancer and other cancer types, the cause of pain is usually pain signals sent from the celiac plexus (Ambai et al. 2021). Sensory nerve endings are located in the pancreatic parenchyma, and these nerves pass through the celiac ganglion without synapses, thus causing pain in pancreatic cancer (Dobosz et al. 2016). With the neurolysis of the celiac plexus, the nerves are damaged. The patient is prevented from feeling pain, or the pain is temporarily blocked by blocking the celiac plexus (Dobosz et al. 2016, Cornman-Homonoff et al. 2017)

Table 1. Formed Cancer of The Head Pancreas

Symptoms	Diseases (%)
Weight Loss	92
Jaundice	82
Pain	72
Anorexia	64
Dark Urine	63
Light Color Stool	62
Nausea	45
Vomiting	37
Fatigue	35

Table 2. Formed Cancer of The Neck and Tail of The Pancreas

Symptoms	Diseases (%)
Weight Loss	100
Pain	87
Nausea	43
Weakness	42
Vomiting	37
Anorexia	33
Constipation	27
Food Intolerance	7
Jaundice	7

Diagnosis of solid pancreatic mass is made by transabdominal ultrasound, endoscopic ultrasound (EUS), multi-detector computed tomography (MDCT), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT), and cross-section imaging methods (Pietryga et al. 2015). Early diagnosis of cancer, which is increasing rapidly nowadays, plays a vital role. Active in the body, especially in pancreatic cancer disease designing a biosensor for the determination of biomarkers that are known to increase It is important and very advantageous. Molecular biomarkers, particularly cancer initiation and progression for strategies to be developed for early detection of cancer it will be useful. Trace of proteins found in serum that are specific to certain types of cancer determination of the amount of tumor, such as carcinoembryonic antigen and alpha-fetoprotein started with the development of determinants. Immunodiffusion and then RIA and ELISA The use of these techniques has led to the discovery of many serum tumor markers, many of them have come into routine use. However, the disadvantage of such determinants is limited their specificity and sensitivity. In recent years, serum or with the understanding of tumor-specific molecular changes in their plasma, cancer a new era begins in diagnosis. Molecular biomarkers, especially cancer finding those associated with initiation and progression is essential for early detection of cancer. It will be useful for developing strategies.

With the discovery of biological molecules that increase in the presence of pancreatic cancer, it is aimed to detect pancreatic cancer at an early stage with the development of biosensors that detect these biomarkers (Ibanez-Redin et al. 2015). Looking at the literature, HSP70 protein in urine bladder urothelial cancer, prostate cancer, pancreatic cancer, breast cancer, endometrial it has also been used as a biomarker in cancer types such as cancer and liver cancer (K. Dutta et al. 2012) .

Biosensors are devices that detect the change that occurs due to a biological or biochemical reaction and can detect the presence/absence of a biological element by converting this change into a series of signals (Szunerits et al. 2018, Cesewski et al. 2020). A biosensor comprises three fundamental components: a biological recognition element (bioreceptor), a converter that converts the change caused by the response into a signal, and a measuring device that detects the signal's strength (Aydın et al. 2019). Biosensors are classified according to the type of bioreceptor or transducer. Different sensors are created with biomolecules

such as enzymes, antibodies, cells, aptamers, or single-stranded DNA. The target recognizes the analyte and binds specifically (Aydın et al. 2019, Strehlitz et al. 2008). According to the type of converter; It is divided into electrochemical systems (amperometric, impedimetric, potentiometric, voltammetric, ion charge or field-effect transistors), optical systems (interferometry, luminescence, etc.), mass change sensing systems, magnetic systems, thermal systems and piezoelectric systems (Torequl Islam, 2017, Piroozmand et al. 2020). Biosensors should have features such as high sensitivity, selectivity, reproducibility, stability, and correct post-processing results (Cornman-Homonoff et al. 2017). The biological recognition element must remain immobile on the surface of the biosensor. This process is called immobilization. The immobilization process is carried out by creating hydrogen bonds, van der Waals interactions, hydrophobic forces, or ionic forces that may occur between the surface and the biological recognition element (Ahmadi et al. 2020).

2. Biomarkers Helping Early Diagnosis of Pancreatic Cancer

It is of great importance to illuminate the pathways that play a role in the initiation and progression of pancreatic cancer. By detecting the molecules produced by cancer cells, the presence and severity of cancer can be measured (Moschovis et al. 2016). The main ones of these molecules are; long noncoding RNAs(lncRNAs) (Ghafouri-Fard et al. 2021), MUC1 (Cao et al. 2017, Yokoyama et al. 2016, Sierzega et al. 2016), MUC4 (Yokoyama et al. 2016, Sierzega et al. 2016), MUC5AC (Sierzega et al. 2016), miR-21 and miR-155 (Ideno et al. 2020), alpha-enolase (Sun et al. 2017), CCT8 (Liu et al. 2019), CTSL (cathepsin L) (Singh et al. 2014), CEACAM (Simeone et al. 2007), osteopontin (Simeone et al. 2007), macrophage inhibitor cytokine-1 (MIC-1) (Koopmann et al. 2004), fucosylated haptoglobin (Fuc-Hpt) (Miyoshi et al. 2016), carbohydrate antigen 19 - 9 (CA19-9) (Li et al. 2021) and alteration of the microbiome in the pancreas (Goonetilleke et al. 2007). Appropriate biosensor studies that enable pancreatic diagnosis can be performed with this biomarker. It aims to detect cancer at an early stage.

2.1. Biosensors for Detection of Pancreatic Cancer

The health system aims to increase the quality of life of individuals by identifying diseasespecific markers. Therefore, a cost-effective and functional method is needed (Ye et al. 2017). Enzyme-linked immunosensor testing (ELISA) is widely used in the detection of biomarkers (Ye et al. 2017, Li et al. 2017). ELISA is a method that is based on signal generation using biological enzymes such as horseradish peroxidase (HRP) or alkaline phosphatase (ALP) and provides quantitative measurement by detecting the color change resulting from interaction (Ye et al. 2017, Khodashenas et al. 2019). A study was conducted to detect Fuc-Hpt, a marker of pancreatic cancer, by ELISA. In this study, a molecule called Aleuria aurantia lectin (AAL), which recognizes all kinds of fucosylation, and AAL-antibody and AAL-reactive structures were used to detect the presence of Fuc-Hpt. It has been determined that Fuc-Hpt is produced ten times more in patients with pancreatic cancer, according to the ELISA test performed on patients with healthy people (Miyoshi et al. 2016). However, molecules such as enzymes (Ye et al.

2017)/antibody and antigen (Zhao et al. 2019)/protein (Gunawan et al. 2018) used in the ELISA method can be easily degraded due to external factors (Li et al. 2017). Therefore, standard ELISA is insufficient for detecting complex and very small molecules, especially cancer markers (Li et al. 2017). The first method used in the diagnosis of pancreatic cancer is ELISA, however, this method is not sensitive and cannot detect proteins in the later stages of cancer. Therefore, one-step devices that can provide faster results, are cheaper and detect even small amounts of markers are preferred (Wang, 2006). Devices such as biosensors play an important role in the early detection of pancreatic cancer and other cancers because detecting cancer at an early stage allows for improving the treatment of the disease and the mortality rate (Blum et al. 2014). CA19-9 is the only biomarker specifically recommended for pancreatic cancer by the National Comprehensive Cancer Network guidelines (Meng et al. 2017). However, approximately 20% of people with pancreatic cancer have little or no expression of the CA19- 9 marker (Luo et al. 2017). The reason for this is that people who do not have the Lewis gene, which constitutes the Lewis (-) blood group system, do not secrete CA19-9 at all or very little (Luo et al. 2017, Tsai et al, 2020). Although this situation creates a negative situation for CA19-9, CA19-9 plays an important role in the detection of pancreatic cancer. Various biosensor studies have been carried out for the detection of CA19-9.

2.2 Immunosensors for Diagnosing Pancreatic Cancer

An immune sensor consists of a sensing element and a transducer. Detection is achieved by immobilizing antigen-antibodies on the biosensor surface. The transducer detects the interaction of antibodies with antigens and converts it into a measurable signal. According to the biosensor transducer, optical immunosensors are divided into several classes, such as electrochemical immunosensors (Justino et al. 2016, Zhu et al. 2019). Electrochemical immunosensors are immunosensors in which the interaction of the antibody and antigen immobilized on the electrode surface is converted into an electrochemical signal. Its major advantages are high specificity and good stability against small amounts of the analyte (Justino et al. 2016). Optical immunosensors have low signal detection and remote signal capture. An optical signal (fluorescent or colored) is produced due to antibody-antigen interaction in optical immunosensors, and the medium's optical properties are changed. Optical changes that occur after antibody-antigen interaction are detected by a photodetector and converted into an electrical signal (Justino et al. 2016). CA19-9, a pancreatic cancer marker, has been detected using immunosensors (Soares et al. 2018). In a study, immunosensors were created using a simple film architecture to detect CA19- 9 biomarkers using electrical impedance spectroscopy. The designed electrode surface has a single layer coated with active anti-CA19-9. Serum samples from patients successfully determined CA19-9 levels. Thus, it has been proven that pancreatic cancer can be detected quickly and simply with high sensitivity (Soares et al. 2018). Screen-printed electrodes modified with nanostructured carbon nano-onion films have been developed that can detect CA19-9 even at low concentrations (Ibanez-Redin et al. 2019). Carbon nano corms (CNOs) are from the fullerene family and consist of hemispherical, polyhedral graphite layers close to each other

(Mykhailiv et al. 2019). Besides showing high compatibility with protein-derived biomolecules such as peptides, glycopeptides, and proteins, it may also allow their use as intracellular carriers (D'amora et al. 2019). For the detection of CA19-9, CNOs, silver (Ag) screen-printed nested electrodes (SPIDEs) modified with graphene oxide (GO) films were prepared and an immunosensor was formed with them (Ibanez-Redin et al. 2019). It has been a simple, reproducible detection method that detects CA19-9 with high specificity (Ibanez-Redin et al. 2019)

Materials from natural sources such as nanomaterials, graphene (Xie et al. 2011), carbon nanotubes (CNTs) (Huang et al. 2015), metallic nanoparticles (Anik et al. 2016), chitosan (El-dib et al. 2014) that can be used in immunosensors serve as a matrix to immobilize biomolecules and increase the sensitivity by increasing the measured signal (Soares et al. 2017). Since gold nanoparticles (AuNPs) generate higher electric current, they provide more active sites in a single recognition reaction and are used to amplify the analytical signal (Cao et al. 2011). An immunosensor has been developed in which polymer nanofibers modified with AuNPs are used as the matrix for the immobilization of anti-CA19-9 antibodies using electrochemical impedance spectroscopy (Soares et al. 2017). It showed high sensitivity in detecting CA19-9 at different concentrations and binds irreversibly to CA19-9 with high sensitivity, selectivity, and antigen-antibody interaction (Soares et al. 2017).

Electrochemiluminescence (ECL) allows electron transfer on the electrode surface and creates excited states that emit light while electron transfer reactions occur (Richter, 2004). The resulting light signal is converted into an electrical signal via a photomultiplier tube (PMT) and then recorded in a computer. There are many application areas such as electrochemiluminescences, DNA detection (Wei et al. 2019), microRNA detection (Liu et al. 2018), and fingerprint detection (Wei et al. 2019). Another method used to differentiate between different types of cancer by exosomal protein marker profiling is high sensitivity ECL. It can distinguish even small differences between other high-sensitivity exosomal protein markers (Wei et al. 2019). An ECL immunosensor was established to detect exosomes by interacting AuNPs loaded on the metal-organic framework (MOF) and various conjugated polymer dots (Pdot). Also, the ECL immunosensor can detect exosomes produced by PANC -1 cells at low concentrations. The biosensor has good potential for clinical diagnosis (Wei et al. 2019). PEAK1, another marker of pancreatic cancer, is found at high rates in malignancies and leads to the growth and metastasis of PDAC (Kelber et al. 2020). This immunosensor design developed an electrochemical biosensor using gold nanoparticles labeled anti-PEAK1 probes. With the developed biosensor, a low-cost and successful PEAK1-specific immunosensor was designed for the early detection of pancreatic cancer (Prasad et al. 2020).

2.3 Aptasensors for Diagnosing Pancreatic Cancer

Aptamers are single-stranded DNA (ssDNA), RNA, or modified nucleic acids that have the ability to bind with high affinity and high specificity to various ions, large proteins, living cells and small organic molecules (Kaur et al. 2018, Shangguan et al. 2006). Aptamers are target tools for early cancer detection with

many advantages such as high tissue penetration, rapid production process, low synthesis cost, low immunogenicity, thermal stability, and ease of labeling. So, they are potential molecules to overcome PDAC therapy and diagnosis challenges (Li et al. 2020). As aptamer-based biosensors, aptasensors show excellent specific binding properties for selecting target molecules. Therefore, aptasensors are preferred over antibody-based biosensors (Sharma et al. 2022).

When aptamers bind to target molecules, their conformation changes. This property has played a key role in target identification. Aptasensors can have electrochemical, optical, and calorimetric properties (Li et al. 2016). A SERS calorimetric bimodal aptasensor has been developed for the detection of MUC1, a marker of pancreatic cancer (Li et al. 2020). In this aptamer-based biosensor, MUC1-specific aptamer functionalized nanobeads were used. It detected MUC1 in a mixed molecule environment using gold-silver core-shell nanoparticles in SERS. Calorimetric SERS probes were used to report signals simultaneously. The designed aptasensor can determine the level of MUC1 in serum samples. It has high sensitivity and allows quantitative measurement of MUC1 (Li et al. 2020). Aptamer-based biosensors are non-invasive devices for early diagnosis of PDAC (Li et al. 2020).

2.4 SERS Biosensors in the Diagnosis of Pancreatic Cancer

Raman spectroscopy relies on inelastic light scattering on the sample. Natural fingerprint vibration information is created on the sample with factors such as Raman spectrum components, symmetry, and environment (Zong et al. 2018). Raman spectroscopy determines chemical elements, molecular structure, conformations, and intermolecular interactions and shows very good results (Zong et al. 2018). Raman spectroscopy is a promising technique with very good chemical properties and specificity to identify the analyte in mixtures of various substances. It has poor signal transmission in water and can be easily studied in aqueous solutions (Zong et al. 2018, Ambartsumyan et al. 2020). To increase the sensitivity of Raman spectroscopy, surface-enhanced Raman spectroscopy (SERS) has been developed on Ag metal surfaces and has greatly increased the sensitivity of Raman spectroscopy (Li et al. 2016). A dual SERS biosensor has been designed to detect microRNAs in exosome and blood plasma residues in the diagnosis of pancreatic cancer (Thind&Wilson, 2016). MiRNAs that increase in the presence of pancreatic cancer, such as miR-21, and miR-155 (Ideno et al. 2020), or in the presence of other cancers, are an important part of exosomal transport (Pang et al. 2019). Tumor miRNAs transmitted by exosomes stimulate the microenvironment and cause tumor progression through angiogenesis (Thind&Wilson, 2016). Therefore, miRNAs are also important biomarkers for the early detection of cancer (Ma et al. 2018). Compared with free miRNAs in serum and exosomal miRNAs, exosomal miRNAs are not inhibited by RNase and are more stable in peripheral blood (Pang et al. 2019). A single-step biosensor study was conducted to detect miRNAs, and a DSN-supported dual SERS biosensor was used in this study (Pang et al. 2019). A biosensor with a DSNsupported recycling signal supported by a dual SERS biosensor with Fe3O4 Ag-SERS assembly, which can detect the analyte even at very low

concentrations, has been created (Pang et al. 2019).

2.5 Electrochemical Biosensors for the Diagnosis of Pancreatic Cancer

Proteases carry out proteolysis, which is one of the biological catalytic reactions. It also controls hysiological processes essential for life, such as proteolysis, digestion, apoptosis, wound healing, and protein and organelle recycling (Eatemadi et al. 2017, Gurumallesh et al. 2019, Turk et al. 2012). There are six protease groups, namely serine, cysteine, glutamic acid (Yang et al. 2009), threonine, aspartate, and metalloproteases (Eatemadi et al. 2017, Turk et al. 2012), Based on the nature of the key amino acid in the active site of the protease and the cleavage mechanism of the peptide bond, and on different catalytic mechanisms (Eatemadi et al. 2017, Turk et al. 2012). In proteolysis, the peptide bond at the carbonyl group of the peptide is hydrolyzed and proteases have a wide range of enzymes (Li et al. 2020). Trypsin is in the serine protease group (Olsen et al. 2004) and is produced by the pancreas (Yang et al. 2009). Trypsin hydrolyzes peptide bonds at the C-terminus of arginine or lysine (Olsen et al. 2004). Trypsin is produced in the pancreas in the form of trypsinogen, if it was not produced in the form of trypsinogen, it could cause serious damage to the pancreas. Therefore, detection of trypsin in serum or urine can be presented as a simpler, useful, and safe method for inhibitör screening (Lin et al. 2019). The presence of trypsin in pancreatic cell lysates plays an important role in the diagnosis of chronic pancreatic diseases (Wu et al. 2014). Binary fluorescent isothiocyanate (FITC) and biotin-modified peptides were immobilized on the surface of magnetic microbeads. Mbs were captured by a magnetic field on the screen-printed electrode surface. The biosensor is based on enzymatic labeling of MB's with the Fab region of the anti-fluorescein antibody conjugated with HRP. In the presence of the HRP enzymatic substrate labeled to MBs, Ag showed amperometric results against the reference electrode. The detection of trypsin in the cancerous pancreatic site with high selectivity and sensitivity has been quantified (Munoz-San Martin et al. 2020).

There are many types of miRNAs that occur in the presence of pancreatic cancer. miR-196b is found at high levels in blood serum in the presence of pancreatic cancer. It has been found to cause differentiation and metastasis of cells. Also, miR-196b is an important biomarker in pancreatic cancer (Wang et al. 2017). To detect miR-196b, a biosensor with an isothermal, dual-signal amplification strategy was developed to convert the signals into electrochemical signals. A polypodamine-gold nanoparticle composite modifier was used as a disposable screen-printed
electrode (Jain et al. 2008). A sensitive biosensor that can detect even very small amounts of miR-196b with high specificity has been developed and shows promise in the diagnosis of pancreatic cancer (Chen et al. 2021).

2.6 Highly Specific Plasmonic Biosensors for Detection of Pancreatic Cancer

The strongly enhanced surface plasmon resonance of noble metal nanoparticles at optical frequencies makes the noble nanoparticles excellent scatterers and absorbers of visible light (Jain et al. 2006). This is called localized surface plasmon resonance

(LSPR) oscillation, and this electronic oscillation creates an intense electric field around the metal particle. It can simply be visualized as a photon limited by the size of the nanostructure (Jain et al. 2006). Solid-state plasmonic biosensors have been produced for the label-free detection of microRNAs involved in pancreatic cancer (Joshi et al. 2014). A plasmonic biosensor was constructed by hybridizing PDAC-related miRNAs with complementary single-stranded DNAs functionalized to the surface of gold nanoprisms attached to the glass substrate and monitoring the LSPR dipole peak. By adding RNA duplex cleavage enzymes, the sensor can be re-sensed. Therefore it is a biosensor with high reproducibility (Joshi et al. 2014).

3. CONCLUSIONS

With the early detection of other types of cancer, such as pancreatic cancer, the survival time of patients increases significantly. This study includes biomarkers for early detection of pancreatic cancer and biosensor studies conducted in recent years. There were many biomarkers as markers of pancreatic cancer. Many different biosensor studies have been and continue to be done to detect these biomarkers. Among the biosensor types, electrochemical and optical biosensors showed much greater sensitivity. The analyte detection limit of the developed biosensors is slightly higher than the samples taken from the patients. Therefore, sometimes accurate results may not be obtained from biosensors due to insufficient analyte. Although CA19-9 is the best known pancreatic cancer biomarker, it is increased even in the presence of other cancer types. Therefore, it is not a very specific biomarker for the early detection of pancreatic cancer. In future studies, biosensor studies to detect more specific molecules such as miRNAs and exosomes that occur in the presence of pancreatic cancer may yield more sensitive and specific results. Since more clear results can be obtained in biosensor studies that can detect more than one biomolecule released in the presence of pancreatic cancer, it is expected that studies on this subject will increase.

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