File name: PepTenChip-IPS2019Eng-CN—KR—JP3

Dear all

We are pleased to send you a reprints of PepTenChip® as a preliminary detection results on human body fluids. Just Today electrically published.

Nokihara K, etal., *Peptide Science 2018*, page 20-21, 2019

Unique and innovative biodetection system using structured and labeled peptide microarrays in combination with imaging and multivalent analyses towards diagnostics not depending on bio-markers

Please find the reprint involving Japanese, Chinese and Korean translated versions.

Japanese of this message is in the attachment file.

Since the development of a unique and novel detection system focusing on diagnostics in the next generation, two decades had been passed. We have devoted a lot of efforts and hence we appreciate numerous supports. Now we are performing experiments of real patients body fluids and focusing on rapid analyses on health care, early detection and prognostics.

The first practical application targeting on human saliva was published as follows. Upon request reprint ca be sent and we do have Japanese version.

Tominaga, Y., Usui, K., Hirata, A., Ito, H. and Nokihara, K., *Bioorganic & Medicinal Chemistry,* **26**, 3210-3216, 2018.
https://doi.org/10.1016/j.bmc.2018.04.049 Applications of a novel bio-detection system to saliva using protein fingerprints with data processing

The introductory and preliminary applications concerning to diseases, neuronal disease and gastric disease has been presented focusing of differentiation in similar diseases which require objective results, further more discrimination in pre-cancer status.

regards

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PepTenChip®

PepTenChip® Background／背景

① **世界でも類を見ない独自のバイオ検出の基盤技術を確立**。当該コンセプト（プロテイン・フィンガープリント法）、新規基板素材に関し、欧州主要国・日本・米国で複数件の特許が認められた。

② 実検体（ヒト体液）を用いてデータマイニング開始、統計学的手法によるデータベースの構築を開始し実用化を進めている。

③ **従来のバイオチップのように1:1対応（抗原抗体反応やマーカー探索）に限定されない**、サロゲートマーカーや新規のマーカー探索にも有用。

④ 当該手法は**マススクリーニング**、健康診断にも威力を発揮できる。また高齢者や動物など健康上の問題点を**医師に口頭で伝えることが困難な例**にも威力を発揮する。

⑤ **標的：**先ずはじめに、**従来法では簡単に検査できない疾病、医師の個人的技量に左右されない客観的判定基準を創生**したい（例：歯周病や多発性硬化症などの神経難疾患）

⑥ **ペプチドアレイのための検出器を自社で設計製作商品化した。**チップをフィルムに例えるなら、その普及でカメラが不可欠である。現在市販されている蛍光検出器は研究用で、高額、大型、メンテナンスも煩雑である。感染の危険があるサンプルを扱う場合、バイオセーフティレベル(BSL) 3 以上の閉鎖空間で使用しなければならない。感染機構あるいは**感染源が未確定**の危険物質も存在する。このため、安価、小型、操作簡便、メンテナンスフリーの蛍光検出装置が必要。**製造と上流特許の実施権のライセンスアウト**計画中。**今後さらに小型化を進め海外で検体実験の際携行機内持ち込み荷物で運搬できるサイズの装置を開発する。**

⑦ PepTenChip®関連製品の販売を開始

PepTenChip®が威力を発揮できる分野

在宅医療：高齢者医療【口がきけない場合＝どこが悪いは自分で言えない】

医師の技量に大きく依存しない客観的な指標

待ち時間 苦痛を避けて診断を避けることを防げる

従来の診断とは競合しない、医師が収益の関係で使用を ためらう理由はない

PepTenChip® may play powerful diagnostic tools: health examination/diagnostics/ prognostics and health management

PepTenChip® can provide the objective indicator not depending on doctor's skill, *i.e.* oral healthcare, neuronal diseases such as multiple sclerosis and early detection of pre-cancer status.

PepTenChip® may allow avoiding to visit clinics/hospitals, because of examination requires long waiting time, accompanies with pain etc.

PepTenChip® may realize: medical treatment of heavy sickness/elderly peoples, especially who cannot explain of their problems to their doctors.

PepTenChip® may not compete conventional diagnostics.

PepTenChip® used by clinicians without hesitation because of the revenue.

Peptide Science 2018, page 20-21, 2019. Proceedings of the 10th International Peptide Symposium, Futaki, S. and Matsuzaki, K (eds) The Japanese Peptide Society

Unique and innovative biodetection system using structured and labeled peptide microarrays in combination with imaging and multivalent analyses towards diagnostics not depending on bio-markers

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Keywords: peptide microarray; multiple sclerosis; gastric diseases

Abstract

A novel biodetection system was evaluated using patient's body fluids towards diagnoses of neuronal and gastric diseases, respectively. The images derived from fluorescent intensity changes were analyzed by statistical methods to show rapid differentiation of neuronal diseases or pre-cancer.

Introduction

The novel biodetection system, designated PepTenChip®, has been developed using labelled structured peptides as capturing molecules. Analyte recognition by capturing peptides immobilized on a chip surface generate fluorescent intensity changes which can be converted into bar-coded, protein fingerprints[1,2]. Using this system differentiation of L-type atypical BSE from classical BSE and scrapie was succeeded[3]. Recently four basic key technologies have been successfully completed: peptide libraries for capture molecules, novel chip material made from amorphous carbon, a high throughput arraying technology, and a portable detector (PepTenCam). Saliva was examined as the first human body fluid for oral healthcare[4] and early detection of periodontal diseases of which the cause is not clarified. The present studies are focusing on rapid differentiation of neuronal and gastric diseases to enable an objective evaluation by clinicians.

Results and Discussion

The novel biodetection system, designated PepTenChip®, has been developed using labelled structured peptides as capturing molecules. Analyte recognition by capturing peptides immobilized on a chip surface generate fluorescent intensity changes which can be converted into bar-coded, protein fingerprints[1,2]. Using this system differentiation of L-type atypical BSE from classical BSE and scrapie was succeeded[3]. Recently four basic key technologies have been successfully completed: peptide libraries for capture molecules, novel chip material made from amorphous carbon, a high throughput arraying technology, and a portable detector (PepTenCam). Saliva was examined as the first human body fluid for oral healthcare[4] and early detection of periodontal diseases of which the cause is not clarified. The present studies are focusing on rapid differentiation of neuronal and gastric diseases to enable an objective evaluation by clinicians.

Multiple sclerosis (MS), an inflammatory autoimmune disorder, is characterized by repeating remission and recurrence without curative therapies (an intractable disease). Hence the cause as well as biomarkers are unknown, although the number of patients increases year by year worldwide. Presently MS-diagnosis is carried out after elimination of other established diseases. However the diagnosis of particular patients is different even among clinical experts. Therefore detection methods to discriminate MS types and related autoimmune diseases are required. Several drugs has been developed although in some case harmful. Rapid and facile objective diagnostics method gives decision of necessary therapy and evaluation of prognostic care. Spinal fluids of patients such as relapse MS, relapse neuromyelitis optica, atypical MS, idiopathic normal pressure hydrocephalus and vascular parkinsonism were collected, applied to the chip and fluorescent intensity changes were measured by a PepTenCam. PCA revealed that each specimen could be classified into 3 distinct groups and typical MS could be discriminated from atypical MS.

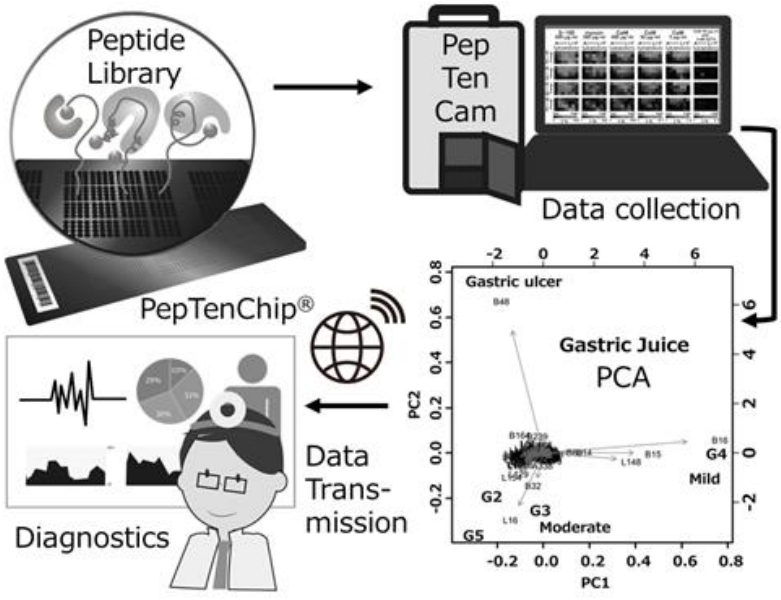

Fig. 1. PepTenChip® system.

Chronic gastritis is a common gastrointestinal disorder that is classified into non-atrophic and atrophic gastritis. The latter is considered as an early stage of cancer and the risk in the carcinogenic rate is high[5]. Currently, diagnosis of gastric diseases are performed by endoscopic examinations with pathological observations. Hence clinicians desire a rapid and simple differentiation method. Gastric juice of several gastric disorders were collected, applied to PepTenChip® and classified by PCA. The obtained groups were distinct among various gastritis types.

The present system (Fig. 1) does not involve the detection of specific molecules such as biomarkers in a 1:1 manner. PCA mediated by the analytes derived more specimens and multivariate analyses are necessary for approval of the Class 1 medical device. Additionally the chip can directly be inserted into MALDI-TOF[6] after fluorescent detection and discovery of undefined materials caused diseases and/or surrogate markers can be possible. Since the system allows noninvasive diagnostics and on-site POC, the PepTenChip® has potential for application in diagnosis of incapacitated patients. Real time and on-site manner serve AI-assisted remote diagnostics and home care.

A part of the present study have been supported by the government of Japan, since the millennium project (MEXT) followed by NEDO, JST, BRAIN/NARO and Cabinet Office. The late stage of this project was partially funded by the New Technology Development Foundation (Tokyo) and Kyoto Industry Support Organization 21

References

1.Nokihara, K., Ohyama, T., Usui, K., Yonemura, K., Takahashi, M. and Mihara, H. (2004) Solid-Phase Synthesis and Combinatorial Chemical Libraries, ed: Epton, R.(ed) Mayflower Scientific, UK, p83-88.
2.Patented in JP (originally JP4562018 and others), US and EU.
3..Kasai, K., Hirata, A., Ohyama, T., Nokihara, K., Yokoyama, T. and Mohri, S. (2012) FEBS Lett., 586, 325-329.
4.Tominaga, Y., Usui, K., Hirata, A., Ito, H. and Nokihara, K. (2018) Bioorganic & Medicinal Chem., 26, 3210-3216.
5.Correa, P., Haenszel, W., Cuello, C., Tannenbaum, S. and Archer M. (1975), Lancet 58-60.
6.Nokihara, K.; Hirata, A.; Ohyama, T.; Sogon, T.; Kawasaki, T. ;Takebayashi, Y.; Oka, Y. Peptide science 2009; (2010) Okamoto K. ed. Japanese Peptide Society. p337-340.

不依赖生物标记的独特和创新的生物检测系统---结构化和标记的肽微阵列结合成像多元分析在疾病诊断的运用

利用病人体液对一种新的生物检测系统进行了评估，这种检测系统分别用于神经疾病和胃病的诊断。采用统计学方法对荧光强度变化后的图像进行分析，用于神经疾病或癌前病变的快速鉴别。

介绍

成功研发了使用标记结构肽作为捕获分子的创新的生物检测系PepTenChip®，通过捕获固定在芯片表面的肽进行分析物识别，并将产生的荧光强度变化转换为蛋白指纹[1,2]。利用该系统成功地将L型非典型BSE与经典BSE和羊瘙痒病进行了鉴别[3]。最近成功完成了四项基本关键技术：捕获分子的肽库、由非晶态碳制成的新型芯片材料、高通量阵列技术和便携式检测器（PepTenCam）。本系统首先检测了唾液这一体液[4]，用于指导口腔保健和早期发现原因不明的牙周疾病。目前的研究主要聚焦在神经系统和消化系统疾病的快速鉴别诊断，以帮助临床医生能够客观评价。

结果和讨论

多发性硬化（MS）是一种炎症性自身免疫性疾病，其特征是反复缓解和复发，没有有效的治疗（一种临床疑难病）。因此，尽管世界范围内的患者数量逐年增加，但原因和生物标志物尚不清楚。目前，MS诊断是在排除其他已确定的疾病后进行诊断的。然而，即使在临床专家中，对特定患者的诊断也是不同的。因此，需要有鉴别多发性硬化症类型和相关自身免疫性疾病的检测方法。该病尽管已经研发出几种治疗药物但有些是有副作用的，因此快速、简便的客观诊断方法为必要的治疗和预后评价提供了决策依据。收集复发性多发性硬化症、复发性视神经脊髓炎、非典型多发性硬化症、特发性正常压力性脑积水、血管性帕金森病等患者的脊髓液，加样于芯片上，用PepTenCam测定荧光强度变化。PCA显示，每个样本可分为独立的3组，并且典型MS可与非典型MS加以鉴别。

慢性胃炎是一种常见的胃肠道疾病，分为非萎缩性和萎缩性胃炎。后者被认为是癌症的早期阶段，致癌率高。目前胃病的诊断是通过内镜检查和病理观察来完成的。因此临床医师需要一种快速而简单的鉴别方法。收集了几种胃病的胃液，应用于PepTenChip®并通过PCA进行分类。结果发现在各种胃炎类型中存在不同。本系统（图1）不是像生物标志物那样以一一对应的方式检测特定分子，分析物介导的PCA衍生出更多的样本和多变量分析对于批准1类医疗器械是必要的。此外，荧光检测后，可将芯片直接插入MALDI-TOF[6]中，以便发现与疾病相关的未知物质和/或潜在标志物。由于该系统允许无创诊断和现场POC，PepTenChip®有可能应用于无行为能力患者的诊断和以实时及现场的方式服务于人工智能辅助远程诊断和家庭护理。

標識ペプチドマイクロアレイを用いた疾患マーカー物質に依存しない診断のためのイメージングと多変量解析を組み合わせた独創的かつ革新的なバイオ検出システム

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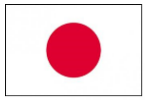
要旨　患者体液(脳脊髄液や胃液)を使用し、新規に開発されたPepTenChip®システムの神経疾患や胃がんの初期の発見に寄与できるか、その実用性を評価した。蛍光強度変化から得られた画像パターンの違いを統計解析処理する画期的な手法は、迅速な検査と客観的診断を実現すると期待される。

キーワード：ペプチドマイクロアレイ、多発性硬化症、胃がん



はじめに

PepTenChip®はペプチド誘導体を捕捉分子として、タンパク質との相互作用を検出するために基板上にマイクロアレイ化したバイオチップである。アレイ化した各種合成ペプチド（捕捉分子）とタンパク質との相互作用（蛍光強度変化）を測定し、これを並べて出力することによりヒートマップが形成される。基板に固定化されるデザイン合成ペプチドの種類を多くすることによって各検体（タンパク質）に対する固有の特徴的画像パターンが得られ、被検体のフィンガープリントとして機能する。[1,2]。構造ペプチドが、実際に非定型BSEと古典的BSEおよびスクレイピーとを区別することに成功した[3]。最近、バイオチップによる生体計測法における4つの基盤技術を完成させた。それらは以下である：①捕捉分子ライブラリー（蛍光標識構造ペプチド3000種を合成・精製・検定）；②新規チップ基板素材（アモルファスカーボン）とその表面化学、表面官能基定量技術；③数百ピコL/spotを基板上に均一にアレイ化するハイスループット技術；④読み取りソフトウエア内蔵の持ち運び可能な小型検出器（PepTenCam）

これらを用いて原因が明らかにされていない歯周病の早期発見を最初のターゲットとし、疾患モデル唾液を検体とする測定を行った[4]。本論文は、臨床医による客観的な評価を可能とするための予備実験であり、神経疾患や胃がんなどの迅速検査に焦点を当て本バイオチップの有用性を試験した。

結果と考察

神経難病である多発性硬化症（Multiple Sclerosis; MS）は、自己免疫疾患で中枢神経炎症性脱髄疾患である。根治が難しく、再発と寛解を繰り返すことが特徴である。原因も疾患バイオマーカーも未知である。患者数は世界中で年々増加している。MSは診断バイオマーカーがなく、時間的、及び空間的多発性を持つ炎症性脱髄疾患から既知の他の炎症性脱髄性疾患を除外することによって診断される疾患である。しかしその診断は難しく、臨床専門家の間でも結果が異なるため、医療現場ではMSのタイプや関連する自己免疫疾患を識別するための検出方法の開発が強く望まれている。MSにはいくつかの治療薬が開発されているが、副作用があり、迅速で容易な客観的診断法は最適な治療法の決定と予後管理に不可欠とされる。我々は再発MS、再発神経脊髄炎、非定型MS、特発性正常圧水頭症および血管性パーキンソニズムなどの患者の脳脊髄液を採取してチップに塗布し、新開発の検出器PepTenCamによって蛍光強度変化を測定した。 主成分分析(Principal Component Analysis; PCA)の結果、各検体は3つの異なるグループに分類でき、典型的なMSは非定型のMSと区別できることが示唆された。一般的な消化器疾患とされる慢性胃炎は、非萎縮性胃炎と萎縮性胃炎とに分類される。後者は胃がんの初期段階であると考えられており、発がん率のリスクが高い[5]。現在、胃疾患の診断は病理学的観察による内視鏡検査によって行われているが、迅速で簡単な識別方法が臨床医から強く望まれている。我々はいくつかの胃疾患の胃液を採取し、PepTenChip®を用いてに分析し、PCAで解析した。その結果、様々な胃炎の患者で分類ができた。

本システム（図１）は、1：1対応で特定の分子を検出するバイオマーカー方法とは異なり、多くの検体とそれらの多変量解析によりもたらされるデータである。一方、捕捉分子によって認識された疾患由来物質やサロゲートマーカーと思われる未知の成分を解析することも可能である。PepTenChip®素材が高い電気伝導性を有するため、サンプルトレイとして用い、直接MALDI-TOFに挿入し検出分子の質量分析や被捕捉分子の部分配列をMS/MS解析することが可能である[6]。本システムの可能性が初めて臨床検体で示された。クラス1医療機器の承認には有効性のデータの蓄積が必須である。本システムは非侵襲診断や臨床現場での診断を可能にするため、リアルタイムでオンサイトな遠隔診断と在宅ケアに有用であると期待される。

本研究の一部は、ミレニアムプロジェクト（文部科学省）、NEDO、JST、BRAIN / NAROや内閣府等、日本政府の支援を得た。また、当該プロジェクトの後期段階では新技術開発財団（東京）と京都産業支援機構21の助成を得た。

【図1および参考文献は原文(英文)参照】

바이오마커에 의존하지 않는 진단을 위하여 미세 배열된 표식자가 붙은 구조 펩타이드에 대한 이미징 및 다면 분석을 조합한 독특하고 혁신적인 바이오 검출 시스템

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새로운 바이오 검출 시스템은 환자의 체액을 사용하여 신경 및 위 질환의 진단을 위해 평가되었습니다. 형광 감도의 변화를 보여주는 이미지를 통계적 방법으로 분석함으로써 신속하게 신경 질환 또는 전이 이전 단계의 암에 대한 차이점을 나타낼 수 있었습니다.

키워드: 펩타이드 마이크로 어레이; 다발성 경화증; 위 질환

소개

PepTenChip®으로 명명된 새로운 바이오 검출 시스템은 포착 분자로서 표지구조 펩타이드를 사용하여 개발되었습니다. 칩 표면에 고정화 된 펩타이드에 의한 검체의 인식 정도를 형광 감도 변화로 나타내게 되며, 이 변화를 바코드 혹은 단백질 지문의 형태로 변환시킵니다[1,2]. 이 시스템을 이용하여 비정형 광우병(L-type atypical BSE)과 정형 광우병(typical, classical BSE)의 구분 및 양의 신경계 질환인 Scrapie의 진단에 성공하였습니다[3]. 최근에 네 가지 기본 핵심 기술, 즉 포착 분자 로서의 펩타이드 라이브러리, 비결정형 탄소로 제작된 새로운 칩 소재, 신속한 처리가 가능한 Array 기술 및 휴대 가능한 검출기(PepTenCam)의 제작이 성공적으로 완료되었습니다. 최초의 인체 체액으로서 타액을 구강 건강 관리[4]를 위한 검체로 사용하였으며, 원인이 밝혀지지 않은 치주 질환의 조기 발견에 사용되었습니다. 현재 연구는 임상의들에 의한 객관적인 평가를 가능하게 하기 위해 신경 및 위 질환의 신속한 차이점을 보여주는데 초점을 두고 있습니다.

결론 및 토론

염증성 자가면역질환인 다발성 경화증(Multiple Sclerosis, MS)은 특별한 치유요법 없이 재발을 반복하는 난치병으로 알려져 있습니다. 따라서 환자 수는 전 세계적으로 증가하고 있지만 질환에 대한 바이오마커 뿐만 아니라 원인도 알려져 있지 않습니다.

Fig. 1.and References see original

현재 MS 진단은 다른 확립된 질병을 제거한 후에 수행됩니다. 그러나 특정 환자의 경우에는 임상 전문가들 사이에서도 판단이 다르게 내려집니다. 따라서 MS 유형 및 이와 관련된 자가면역질환을 식별하기 위한 검출 방법이 필요합니다. 여러 약이 개발되었는데 어떤 경우에는 건강에 해로운 경우도 있습니다. 신속하고 쉬우면서도 객관적인 진단 방법은 필요한 치료의 결정과 치료 예후에 대한 평가를 가능하게 합니다.

재발성 MS, 재발성 시신경척수염(neuromyelitis optica), 비정형 MS, 특발성 정상압 뇌수종 및 혈관 파킨슨병 환자의 척수액을 채취하여 칩에 적용하고 형광 감도의 변화를 PepTenCam으로 측정하였습니다. PCA는 각 표본이 3 개의 구분된 그룹으로 분류될 수 있으며 전형적인 MS는 비정형 MS와 구별될 수 있음을 밝혔습니다.

만성 위염은 비 위축성 및 위축성 위염으로 분류되는 일반적인 위장 장애입니다. 후자는 암의 초기 단계로 간주되며 발암 위험률이 높습니다 [5]. 현재 위 병의 진단은 병리학 적 관찰을 통한 내시경 검사로 이루어집니다. 따라서 임상의는 신속하고 간편한 분별 방법을 원합니다. 여러 위 질환의 위액을 수집하여 PepTenChip®에 적용하고 PCA로 분류했습니다.

수집된 샘플들은 여러가지 위염 유형 군으로 구분이 되었습니다. 본 시스템 (그림 1)은 1:1 방식의 바이오 마커와 같은 특정 분자의 검출을 수반하지 않습니다. 검체에 의해 매개되는 PCA는 더 많은 표본을 필요로 하며, 다면 분석은 1 등급 의료 기기의 승인에 필요합니다. 또한 형광 검출 이후 MALDI-TOF [6]에 칩을 직접 삽입함으로써 알려지지 않은 질병 원인 물질의 발견, 혹은 대리 마커를 탐색할 수도 있습니다.

본 시스템은 비 침습적인 진단 및 현장 POC를 허용하기 때문에 PepTenChip®은 이동이 매우 불편한 환경, 혹은 상태 환자의 진단에 응용 가능성이 있습니다. 실시간 및 현장 방식으로 AI 지원 원격 진단 및 홈 케어 서비스를 제공합니다.

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