様式Ｆ－１９

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研究課題名（和文）　生分解性を有する導電性ポリマーの創出と再生医療への応用

研究課題名（英文）Synthesis, Properties and Applications of Conducting Biomaterial

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研究成果の概要（和文）：

1. エチレングリコール鎖を付加したポリチオフェンと、-OH, -COOH, -NH2 基を導入したポリエチレンジオキシチオフェン（PEDOT）を合成し、その生体適合性を評価した。細胞適合性圧政では、線維芽細胞は接着し増殖した。
2. イニシエーターして臭素を含む PEDOTs を電解重合法によりデポジットした後、高分子ブラシを ATRP 法の応用により調製した。QCM により、調製した高分子ブラシのタンパク質吸着抑制能を確認した。
3. 血中のがん細胞を高感度でキャッチ&リリースできるナノデバイスを開発

研究成果の概要（英文）：

1. Novel oxyhtiophene based conducting polymers with oligoethylene glycol, or functional group such as OH, COOH, NH_2 were synthesized and their cell compatibility was evaluated.
2. Novel EDOT based conducting biointerface with control protein or cell adhesionwas fabricated by conbined electropolymer and surface initated ATRP polymer.
3. Novel thermal responsive silicon nanowire was prepared and was successful applied to selective capture and release cancer cells.

交付決定額

（金額単位：円）

	直接経費	間接経費	合　計
交付決定額	3,400,000	1,020,000	4,420,000

研究分野：総合領域
科研費の分科・細目：人間医工学・医用生体工学・生体材料学
キーワード：Thiophene , conducting polymer, biomaterial

１．研究開始当初の背景

Electrically conductive and biologically active scaffold will provide a unique tool for tissue engineering with the capability to stimulate cells electrically. In this proposal, we would like to fabricate novel cell engineeringed scaffold from oxythiophene based conducting polymers, which features spatial control of chemical functionality and nano-scale topography, tunable mechanical and biodegradable properties.

２．研究の目的

TO develop novel conducting biomaterial for biomedical applications.

３．研究の方法

Synthesis of functional oxythiophene based monomers, and polymerization.
Evaluation of the cell computability of the developed polymers.

４．研究成果

(a) Novel oxyhtiophene based conducting polymers with oligoethylene glycol, or functional group such as OH, COOH, NH_2 were synthesized （scheme 1,2） and their cell compatibility was evaluated (Figure 1).

Scheme 1. Synthesis of oligoehtylene glycol containing polyoxythiophenes

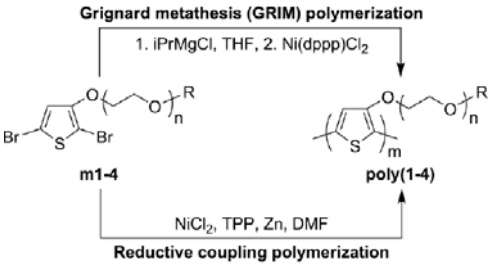


Table 1. Polymerization of **m1-4** by Grignard metathesis polymerization[a] and reductive coupling polymerization[b]

monomer	catalyst	polymer	yield (%)	Mn[c]	Mw/Mn[c]	DP
m1	iPrMgCl, $Ni(dppp)Cl_2$	poly(**1**)-Mg, dark blue	66	2800	1.2	14
m2	iPrMgCl, $Ni(dppp)Cl_2$	Poly(**2**)-Mg, dark blue	48	4800	1.3	17
m1	$NiCl_2$, TPP, Zn	poly(**1**)-Zn, dark red	98	2200	1.1	11
m2	$NiCl_2$, TPP, Zn	poly(**2**)-Zn, dark red	79	2200	1.1	8
m3	$NiCl_2$, TPP, Zn	poly(**3**)-Zn, ferric red	29	2700	1.4	9
m4	$NiCl_2$, TPP, Zn	poly(**4**)-Zn, ferric red	48	3100	1.5	8

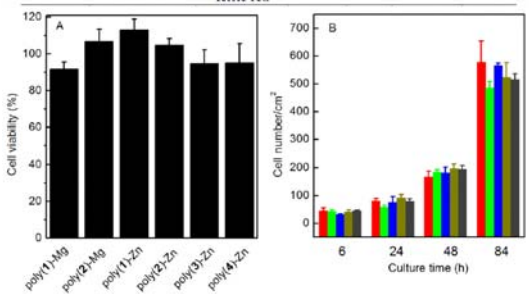
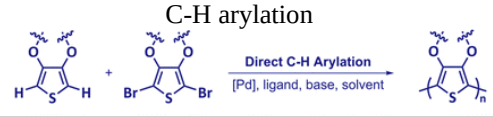


Figure 1. cell viability and cell density on polydioxythiophenes coatings.

Scheme 2. Synthesis of polydioxy thiophene by C-H arylation



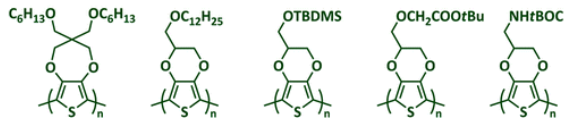


Table 1. Synthesis of Alkyl Group Containing Poly(1–2) by Direct C–H Arylation Polycondensation[a]

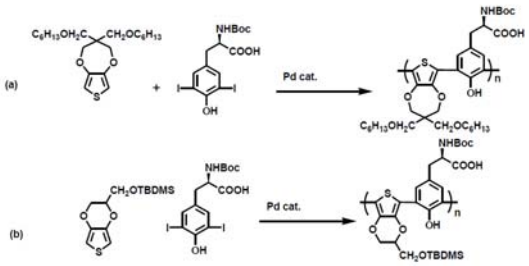
entry	polymer	Pd catalyst	ligand	yield[b] (%)	M_n[c]	PDI	DP[d]
1	poly(1)	$Pd(OAc)_2$	none[e]	60	8800	1.8	25
2	poly(1)	$Pd(OAc)_2$	PPh_3	92	7400	1.4	21
3	poly(1)	$Pd(OAc)_2$	P(*p*-Tol)$_3$	78	6400	1.3	18
4	poly(1)	$Pd(OAc)_2$	P(*o*-PhOMe)$_3$	63	6100	1.9	17
5	poly(1)	$Pd(OAc)_2$	PCy_2-HBF_4	85	9600	1.6	27
6	poly(1)	$Pd(OAc)_2$	$PtBu_2Me$-HBF_4	56	6800	1.7	19
7[f]	poly(1)	$Pd(OAc)_2$(*p*-Tol)	P(*o*-PhOMe)$_3$	91	8400	1.5	22
8	poly(2)	$Pd(OAc)_2$	none[e]	92	3800	1.1	11
9	poly(2)	$Pd(OAc)_2$	PPh_3	85	3900	1.1	12
10	poly(2)	$Pd(OAc)_2$	P(*p*-Tol)$_3$	65	3800	1.1	11
11	poly(2)	$Pd(OAc)_2$	P(*o*-PhOMe)$_3$	–[g]			
12	poly(2)	$Pd(OAc)_2$	PCy_2-HBF_4	–[g]			
13	poly(2)	$Pd(OAc)_2$	$PtBu_2Me$-HBF_4	40	2700	1.1	8
14[f]	poly(2)	$Pd(OAc)_2$(*p*-Tol)	P(*o*-PhOMe)$_3$	85	4800	1.1	14

Table 2. Synthesis of Protected Functional Groups Containing Poly(3–5) by Direct C–H Arylation Polycondensation[a]

entry	polymer	Pd catalyst	ligand	yield[b] (%)	M_n[c]	PDI	DP[d]
1	poly(3)	$Pd(OAc)_2$	none[e]	69	3500	1.1	12
2	poly(3)	$Pd(OAc)_2$	PPh_3	58	2100	1.2	7
3	poly(3)	$Pd(OAc)_2$	P(*p*-Tol)$_3$	62	3300	1.1	12
4	poly(3)	$Pd(OAc)_2$	P(*o*-PhOMe)$_3$	41	3100	1.1	11
5	poly(3)	$Pd(OAc)_2$	PCy_2-HBF_4	45	–[g]		
6	poly(3)	$Pd(OAc)_2$	$PtBu_2Me$-HBF_4	28	–[g]		
7[f]	poly(3)	$Pd(OAc)_2$(*p*-Tol)	P(*o*-PhOMe)$_3$	68	3400	1.1	12
8	poly(4)	$Pd(OAc)_2$	None[e]	93	2700	1.2	10
9	poly(4)	$Pd(OAc)_2$	PPh_3	0			
10	poly(4)	$Pd(OAc)_2$	P(*p*-Tol)$_3$	89	2000	1.1	7
11	poly(4)	$Pd(OAc)_2$	P(*o*-PhOMe)$_3$	11	2100	1.2	7
12	poly(4)	$Pd(OAc)_2$	PCy_2-HBF_4	0			
13	poly(4)	$Pd(OAc)_2$	$PtBu_2Me$-HBF_4	0			
14[f]	poly(4)	$Pd(OAc)_2$(*p*-Tol)	P(*o*-PhOMe)$_3$	0			
15	poly(5)	$Pd(OAc)_2$	none[e]	69	3900	1.2	15
16[f]	poly(5)	$Pd(OAc)_2$(*p*-Tol)	P(*o*-PhOMe)$_3$	67	3200	1.2	12

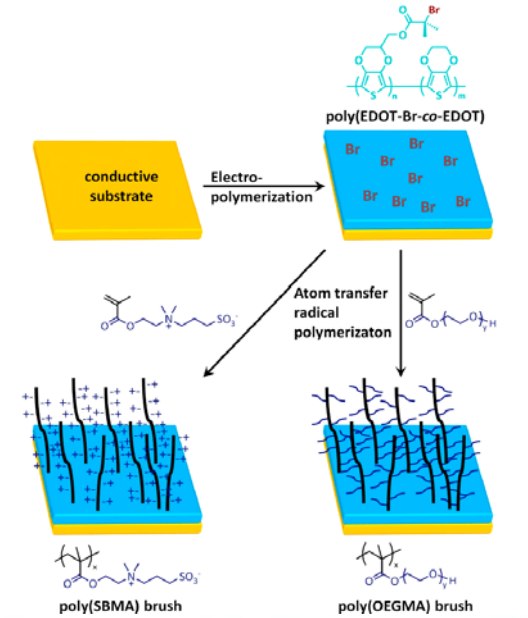
(b)Novel chiral amino acid-based conducting polymer was successfully synthesized by polycondensation of 3,5-diiodo-L-tyrosine with dioxythiophene with moderate molecule weight via direct C-H arylation by using Pd(OAc)2 as catalyst. This novel amino acid based conducting polymers shows potentials applications for tissue engineering.

Scheme 3. Synthesis of amino acid containing chiral conducting polymers



(c)A general approach utilizing electropolymerization to form initiating group (-Br) containing poly(3,4-ethylenedioxythiophen)s (scheme 4) (poly(EDOT)s) is described. After the conducting polymer is deposited, neutral poly((oligo(ethylene glycol) methacrylate), poly(OEGMA), and zwitterionic poly([2-(methacryloyloxy)ethyl]dimethyl-(3-sulfo propyl)ammonium hydroxide), poly(SBMA), brushes are grafted by surface-initiated atom transfer radical polymerization. Quartz crystal microbalance (QCM) experiments confirm protein resistance of poly(OEGMA) and poly(SBMA)-grafted poly(EDOT)s. The protein binding properties of the surface are modulated by the density of polymer brushes, which is controlled by the feed content of initiator-containing monomer (EDOT-Br) in the monomer mixture solution for electropolymerization. Furthermore, these polymer-grafted poly(EDOT)s also prevent cells to adhere on the surface (Figure 2)

Scheme 4. Synthesis of polymer brushes by ATRP on poly(edot)



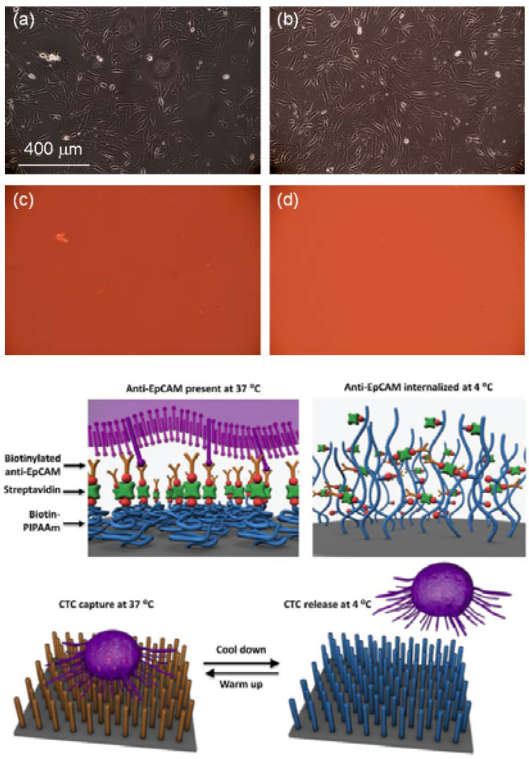
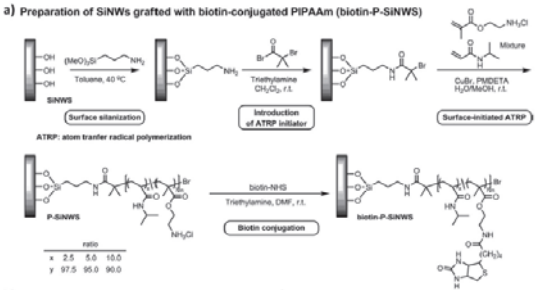


Figure 2. Microscope imageis of NIH3T3 fibroblasts attached on (a) ITO glass, (b) PEDOT coating glass (c) poly(OEGMA) brushes (d) polySBMA brushes

(e) I reported a new nanoscale Velcro-like device that captures and releases tumor cells that have broken away from primary tumors and are circulating in the bloodstream.This new nanotechnology could be used for cancer diagnosis and give insight into the mechanisms of how cancer spreads throughout the body. The device provides a convenient and non-invasive alternative to biopsy, the current method for diagnosis of metastatic cancer. It could enable doctors to detect tumor cells that circulate in cancer patients' blood well before they subsequently colonize as tumors in other organs. The device also enables researchers to keep the tumor cells alive and subsequently study them

Scheme 4. Synthesis of poly(NIPAM) grafted silicon nanowire



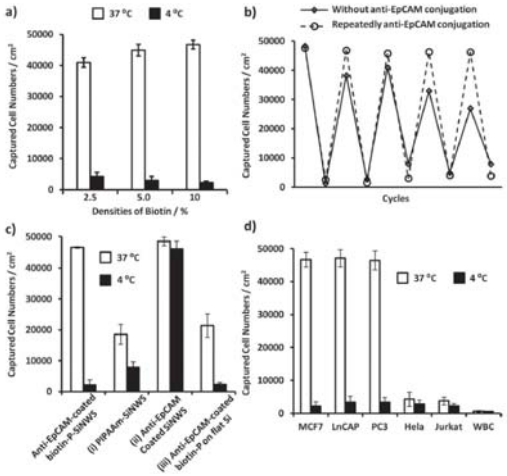


Figure 3. cell capture and release

５．主な発表論文等

（研究代表者、研究分担者及び連携研究者には下線）

〔雑誌論文〕（計　4 件）

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(2) Facile Syntheses of Dioxythiophene-Based Conjugated Polymers by Direct C–H Arylation
Haichao Zhao, Ching-Yuan Liu, Shyh-Chyang Luo, Bo Zhu, Tsai-Hui Wang, Hsiu-Fu Hsu, and Hsiao-hua Yu
Macromolecules, 2012, 45 (19), pp 7783–7790 (peer reviewed)

(3)Polydioxythiophene Nanodots, Nonowires, Nano-Networks, and Tubular Structures: The Effect of Functional Groups and Temperature in Template-Free Electropolymerization
Shyh-Chyang Luo, Jun Sekine, Bo Zhu, **Haichao Zhao**, Aiko Nakao, and Hsiao-hua Yu
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(4)Oligoethylene-Glycol-Functionalized Polyoxythiophenes for Cell Engineering: Syntheses, Characterizations, and Cell Compatibilities
Haichao Zhao, Bo Zhu, Jun Sekine, Shyh-Chyang Luo, and Hsiao-hua Yu
ACS Appl. Mater. Interfaces, 2012, 4 (2), pp 680–686. (peer reviewed)

〔学会発表〕（計　1 件）

(1)**日本化学会**2013.3.22-25,**年会**,立命館大学

Synthesis and properties of novel polydioxyhtiophene via C-H arylation. Haichao Zhao

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