US006591125B1

(12) **United States Patent**
Buse et al.

(10) **Patent No.: US 6,591,125 B1**
(45) **Date of Patent: Jul. 8, 2003**

(54) **SMALL VOLUME IN VITRO ANALYTE SENSOR WITH DIFFUSIBLE OR NON-LEACHABLE REDOX MEDIATOR**

(75) Inventors: **John Bernard Buse**, Chapel Hill, NC (US); **Alan Charles Moses**, Newton Centre, MA (US)

(73) Assignee: **TheraSense, Inc.**, Alameda, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 238 days.

(21) Appl. No.: **09/604,614**

(22) Filed: **Jun. 27, 2000**

(51) **Int. Cl.**[7] **A61B 5/05**
(52) **U.S. Cl.** **600/347**; 600/345; 600/365
(58) **Field of Search** 600/300–301, 600/345, 347, 365, 573; 436/95, 180, 174, 183

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,260,656	A	7/1966	Ross, Jr.
3,653,841	A	4/1972	Klein
3,719,564	A	3/1973	Lilly, Jr. et al.
3,776,832	A	12/1973	Oswin et al.
3,837,339	A	9/1974	Aisenberg et al.
3,972,320	A	8/1976	Kalman
3,979,274	A	9/1976	Newman
4,008,717	A	2/1977	Kowarski
4,016,866	A	4/1977	Lawton
4,055,175	A	10/1977	Clemens et al.
4,059,406	A	11/1977	Fleet
4,076,596	A	2/1978	Connery et al.
4,098,574	A	7/1978	Dappen
4,100,048	A	7/1978	Pompei et al.
4,151,845	A	5/1979	Clemens
4,168,205	A	9/1979	Danninger et al.
4,172,770	A	10/1979	Semersky et al.
4,178,916	A	12/1979	McNamara
4,206,755	A	6/1980	Klein
4,224,125	A	9/1980	Nakamura et al.
4,240,438	A	12/1980	Updike et al.
4,240,889	A	12/1980	Yoda et al.
4,247,297	A	1/1981	Berti et al.
4,271,119	A	6/1981	Columbus
4,318,784	A	3/1982	Higgins et al.
4,340,458	A	7/1982	Lerner et al.
4,356,074	A	10/1982	Johnson
4,365,637	A	12/1982	Johnson
4,366,033	A	12/1982	Richter et al.
4,375,399	A	3/1983	Havas et al.
4,384,586	A	5/1983	Christiansen
4,392,933	A	7/1983	Nakamura et al.
4,401,122	A	8/1983	Clark, Jr.
4,404,066	A	9/1983	Johnson
4,407,959	A	10/1983	Tsuji et al.
4,418,148	A	11/1983	Oberhardt
4,420,564	A	12/1983	Tsuji et al.
4,427,770	A	1/1984	Chen et al.
4,431,004	A	2/1984	Bessman et al.
4,436,094	A	3/1984	Cerami
4,444,892	A	4/1984	Malmros
4,450,842	A	5/1984	Zick et al.
4,461,691	A	7/1984	Frank
4,469,110	A	9/1984	Slama
4,477,314	A	10/1984	Richter et al.
4,483,924	A	11/1984	Tsuji et al.
4,484,987	A	11/1984	Gough
4,522,690	A	6/1985	Venkatasetty
4,524,114	A	6/1985	Samuels et al.
4,526,661	A	7/1985	Steckhan et al.
4,534,356	A	8/1985	Papadakis
4,538,616	A	9/1985	Rogoff
4,543,955	A	10/1985	Schroeppel
4,545,382	A	10/1985	Higgins et al.
4,552,840	A	11/1985	Riffer

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

DD	227 029	A3	9/1985
DE	29 03 216		8/1979
EP	0 048 090	A2	3/1982
EP	0 078 636	A1	5/1983
EP	0 096 288	A1	12/1983
EP	0 125 139	A2	11/1984
EP	0 136 362	A1	4/1985
EP	0 170 375	A2	2/1986
EP	0 080 304	B1	5/1986
EP	0 184 909	A2	6/1986
EP	0 206 218	A2	12/1986
EP	0 230 472	A1	8/1987

(List continued on next page.)

OTHER PUBLICATIONS

Abruña, H. D. et al., "Rectifying Interfaces Using Two–Layer Films of Electrochemically Polymerized Vinylpyridine and Vinylbipyridine Complexes of Ruthenium and Iron on Electrodes," *J. Am. Chem. Soc.*, 103(1):1–5 (Jan. 14, 1981).

Albery, W. J. et al., "Amperometric enzyme electrodes. Part II. Conducting salts as electrode materials for the oxidation of glucose oxidase," *J. Electroanal. Chem. Interfacial Electrochem.*, 194(2) (1 page—Abstract only) (1985).

(List continued on next page.)

Primary Examiner—Robert L. Nasser
Assistant Examiner—Patricia Mallari
(74) *Attorney, Agent, or Firm*—Merchant & Gould P.C.

(57) **ABSTRACT**

A region of skin, other than the fingertips, is stimulated. After stimulation, an opening is created in the skin (e.g., by lancing the skin) to cause a flow of body fluid from the region. At least a portion of this body fluid is transported to a testing device where the concentration of analyte (e.g., glucose) in the body fluid is then determined. It is found that the stimulation of the skin provides results that are generally closer to the results of measurements from the fingertips, the traditional site for obtaining body fluid for analyte testing.

U.S. PATENT DOCUMENTS

4,560,534	A	12/1985	Kung et al.
4,571,292	A	2/1986	Liu et al.
4,573,994	A	3/1986	Fischell et al.
4,581,336	A	4/1986	Malloy et al.
4,595,011	A	6/1986	Phillips
4,595,479	A	6/1986	Kimura et al.
4,619,754	A	10/1986	Niki et al.
4,633,878	A	1/1987	Bombardieri
4,637,403	A	1/1987	Garcia et al.
4,650,547	A	3/1987	Gough
4,654,197	A	3/1987	Lilja et al.
4,655,880	A	4/1987	Liu
4,655,885	A	4/1987	Hill et al.
4,671,288	A	6/1987	Gough
4,679,562	A	7/1987	Luksha
4,680,268	A	7/1987	Clark, Jr.
4,682,602	A	7/1987	Prohaska
4,684,537	A	8/1987	Graetzel et al.
4,685,463	A	8/1987	Williams
4,703,756	A	11/1987	Gough et al.
4,711,245	A	12/1987	Higgins et al.
4,717,673	A	1/1988	Wrighton et al.
4,721,601	A	1/1988	Wrighton et al.
4,726,378	A	2/1988	Kaplan
4,750,496	A	6/1988	Reinhart et al.
4,757,022	A	7/1988	Shults et al.
4,758,323	A	7/1988	Davis et al.
4,759,371	A	7/1988	Franetski
4,759,828	A	7/1988	Young et al.
4,764,416	A	8/1988	Ueyama et al.
4,776,944	A	10/1988	Janata et al.
4,781,798	A	11/1988	Gough
4,784,736	A	11/1988	Lonsdale et al.
4,795,707	A	1/1989	Niiyama et al.
4,805,624	A	2/1989	Yao et al.
4,813,424	A	3/1989	Wilkins
4,815,469	A	3/1989	Cohen et al.
4,820,399	A	4/1989	Senda et al.
4,822,337	A	4/1989	Newhouse et al.
4,830,959	A	5/1989	McNeil et al.
4,832,797	A	5/1989	Vadgama et al.
4,840,893	A	6/1989	Hill et al.
4,848,351	A	7/1989	Finch
4,871,351	A	10/1989	Feingold
4,871,440	A	10/1989	Nagata et al.
4,890,620	A	1/1990	Gough
4,894,137	A	1/1990	Takizawa et al.
4,897,162	A	1/1990	Lewandowski et al.
4,897,173	A	1/1990	Nankai et al.
4,909,908	A	3/1990	Ross et al.
4,911,794	A	3/1990	Parce et al.
4,919,141	A	4/1990	Zier et al.
4,919,767	A	4/1990	Vadgama et al.
4,923,586	A	5/1990	Katayama et al.
4,927,516	A	5/1990	Yamaguchi et al.
4,935,105	A	6/1990	Churchouse
4,935,345	A	6/1990	Guilbeau et al.
4,936,956	A	6/1990	Wrighton
4,938,860	A	7/1990	Wogoman
4,942,127	A	7/1990	Wada et al.
4,945,045	A	7/1990	Forrest et al.
4,950,378	A	8/1990	Nagata
4,953,552	A	9/1990	DeMarzo
4,968,400	A	11/1990	Shimomura et al.
4,970,145	A	11/1990	Bennetto et al.
4,974,929	A	12/1990	Curry
4,986,271	A	1/1991	Wilkins
4,994,167	A	2/1991	Shults et al.
5,034,192	A	7/1991	Wrighton et al.
5,070,535	A	12/1991	Hochmair et al.
5,078,854	A	1/1992	Burgess et al.
5,082,550	A	1/1992	Rishpon et al.
5,082,786	A	1/1992	Nakamoto
5,089,112	A	2/1992	Skotheim et al.
5,094,951	A	3/1992	Rosenberg
5,096,560	A	3/1992	Takai et al.
5,096,836	A	3/1992	Macho et al.
5,101,814	A	4/1992	Palti
5,108,564	A	4/1992	Szuminsky et al.
5,109,850	A	5/1992	Blanco et al.
5,120,420	A	6/1992	Nankai et al.
5,120,421	A	6/1992	Glass et al.
5,126,034	A	6/1992	Carter et al.
5,126,247	A	6/1992	Palmer et al.
5,130,009	A	7/1992	Marsoner et al.
5,133,856	A	7/1992	Yamaguchi et al.
5,140,393	A	8/1992	Hijikihigawa et al.
5,141,868	A	8/1992	Shanks et al.
5,161,532	A	11/1992	Joseph
5,165,407	A	11/1992	Wilson et al.
5,168,046	A	12/1992	Hamamoto et al.
5,174,291	A	12/1992	Schoonen et al.
5,185,256	A	2/1993	Nankai et al.
5,192,415	A	3/1993	Yoshioka et al.
5,192,416	A	3/1993	Wang et al.
5,198,367	A	3/1993	Aizawa et al.
5,200,051	A	4/1993	Cozzette et al.
5,202,261	A	4/1993	Musho et al.
5,205,920	A	4/1993	Oyama et al.
5,206,145	A	4/1993	Cattell
5,208,154	A	5/1993	Weaver et al.
5,217,595	A	6/1993	Smith et al.
5,227,042	A	7/1993	Zawodzinski et al.
5,229,282	A	7/1993	Yoshioka et al.
5,250,439	A	10/1993	Musho et al.
5,262,035	A	11/1993	Gregg et al.
5,262,305	A	11/1993	Heller et al.
5,264,103	A	11/1993	Yoshioka et al.
5,264,106	A	11/1993	McAleer et al.
5,271,815	A	12/1993	Wong
5,272,060	A	12/1993	Hamamoto et al.
5,278,079	A	1/1994	Gubinski et al.
5,286,362	A	2/1994	Hoenes et al.
5,286,364	A	2/1994	Yacynych et al.
5,288,636	A	2/1994	Pollmann et al.
5,293,546	A	3/1994	Tadros et al.
5,310,885	A	5/1994	Maier et al.
5,320,725	A	6/1994	Gregg et al.
5,326,449	A	7/1994	Cunningham
5,337,747	A	8/1994	Neftel
5,352,348	A	10/1994	Young et al.
5,356,786	A	10/1994	Heller et al.
5,364,797	A	11/1994	Olson et al.
5,368,028	A	11/1994	Palti
5,372,133	A	12/1994	Hogen Esch
5,378,628	A	1/1995	Grätzel et al.
5,380,422	A	1/1995	Negishi et al.
5,382,346	A	1/1995	Uenoyama et al.
5,387,327	A	2/1995	Khan
5,390,671	A	2/1995	Lord et al.
5,391,250	A	2/1995	Cheney, II et al.
5,393,903	A	2/1995	Gratzel et al.
5,395,504	A	3/1995	Saurer et al.
5,411,647	A	5/1995	Johnson et al.
5,413,690	A	5/1995	Kost et al.
5,422,246	A	6/1995	Koopal et al.
5,437,973	A	8/1995	Vadgama et al.
5,437,999	A	8/1995	Diebold et al.
5,478,751	A	12/1995	Oosta et al.

5,496,453	A		3/1996	Uenoyama et al.
5,497,772	A		3/1996	Schulman et al.
5,501,956	A		3/1996	Wada et al.
5,507,288	A		4/1996	Böcker et al.
5,508,171	A		4/1996	Walling et al.
5,514,253	A		5/1996	Davis et al.
5,520,787	A		5/1996	Hanagan et al.
5,525,511	A		6/1996	D'Costa
5,526,120	A		6/1996	Jina et al.
5,531,878	A		7/1996	Vadgama et al.
5,552,027	A		9/1996	Birkle et al.
5,556,524	A		9/1996	Albers
5,565,085	A		10/1996	Ikeda et al.
5,567,302	A		10/1996	Song et al.
5,568,806	A		10/1996	Cheney, II et al.
5,569,186	A		10/1996	Lord et al.
5,575,895	A		11/1996	Ikeda et al.
5,580,527	A		12/1996	Bell et al.
5,582,184	A		12/1996	Erickson et al.
5,582,697	A		12/1996	Ikeda et al.
5,582,698	A		12/1996	Flaherty et al.
5,586,553	A		12/1996	Halili et al.
5,589,326	A		12/1996	Deng et al.
5,593,852	A		1/1997	Heller et al.
5,596,150	A		1/1997	Arndt et al.
5,617,851	A		4/1997	Lipkovker
5,628,890	A		5/1997	Carter et al.
5,650,062	A		7/1997	Ikeda et al.
5,651,869	A		7/1997	Yoshioka et al.
5,660,163	A		8/1997	Schulman et al.
5,670,031	A		9/1997	Hintsche et al.
5,680,858	A		10/1997	Hansen et al.
5,682,233	A		10/1997	Brinda
5,695,623	A		12/1997	Michel et al.
5,695,947	A		12/1997	Guo et al.
5,708,247	A		1/1998	McAleer et al.
5,711,861	A		1/1998	Ward et al.
5,711,862	A		1/1998	Sakoda et al.
5,720,862	A		2/1998	Hamamoto et al.
5,727,548	A		3/1998	Hill et al.
5,741,211	A		4/1998	Renirie et al.
5,741,688	A		4/1998	Oxenb et al.
5,746,217	A		5/1998	Erickson et al.
5,770,028	A		6/1998	Maley et al.
5,791,344	A		8/1998	Schulman et al.
5,804,048	A		9/1998	Wong et al.
5,820,570	A		10/1998	Erickson et al.
5,830,341	A		11/1998	Gilmartin
5,834,224	A		11/1998	Ruger et al.
5,837,454	A		11/1998	Cozzette et al.
5,842,983	A		12/1998	Abel et al.
5,846,702	A		12/1998	Deng et al.
5,846,744	A		12/1998	Athey et al.
5,857,983	A		1/1999	Douglas et al.
5,879,311	A		3/1999	Duchon et al.
6,004,441	A		12/1999	Fujiwara et al.
6,033,866	A		3/2000	Guo et al.
6,071,391	A		6/2000	Gotoh et al.
6,258,229	B1	*	7/2001	Winarta et al. 204/403.04
6,332,871	B1	*	12/2001	Douglas et al. 600/583

FOREIGN PATENT DOCUMENTS

EP	0 241 309	A3	10/1987
EP	0 245 073	A2	11/1987
EP	0 278 647	A2	8/1988
EP	0 286 084	A2	10/1988
EP	0 359 831	A1	3/1990
EP	0 368 209	A1	5/1990
EP	0 390 390	A1	10/1990
EP	0 400 918	A1	12/1990
EP	0 470 290	A1	2/1992
EP	0 255 291	B1	6/1992
EP	0 127 958	B2	4/1996
EP	0 781 406	B1	5/1998
GB	1394 171		5/1975
GB	2 073 891	A	10/1981
GB	2 154 003	B	8/1985
GB	2 204 408	A	11/1988
JP	54-41191		4/1979
JP	55-10581		1/1980
JP	55-10583		1/1980
JP	55-10584		1/1980
JP	55-12406		1/1980
JP	56-163447		12/1981
JP	57-70448		4/1982
JP	60-173457		9/1985
JP	60-173458		9/1985
JP	60-173459		9/1985
JP	61-90050		5/1986
JP	62-85855		4/1987
JP	62 114747		5/1987
JP	63-58149		3/1988
JP	63-128252		5/1988
JP	63-139246		6/1988
JP	63-294799		12/1988
JP	63-317758		12/1988
JP	1-114746		5/1989
JP	1-114747		5/1989
JP	1-134244		5/1989
JP	1-156658		6/1989
JP	2-62958		3/1990
JP	2-120655		5/1990
JP	2-287145		11/1990
JP	2-310457		12/1990
JP	3-26956		2/1991
JP	3-28752		2/1991
JP	3-202764		9/1991
JP	5-72171		3/1993
JP	5-196595		8/1993
SU	1281988	A1	1/1987
WO	WO 85/05119		11/1985
WO	WO 89/08713		9/1989
WO	WO 90/05300		5/1990
WO	WO 91/04704		4/1991
WO	WO 91/09139		6/1991
WO	WO 92/13271		8/1992
WO	WO 94/20602		9/1994
WO	WO 94/27140		11/1994
WO	WO 95/02817		1/1995
WO	WO 97/00441		1/1997
WO	WO 97/18464		5/1997
WO	WO 97/19344		5/1997
WO	WO 97/42882		11/1997
WO	WO 97/42883		11/1997
WO	WO 97/42886		11/1997
WO	WO 97/42888		11/1997
WO	WO 97/43962		11/1997
WO	WO 98/35225		8/1998
WO	WO 99/08106		2/1999
WO	WO 99/30152		6/1999

OTHER PUBLICATIONS

Albery, W. J. et al., "Amperometric Enzyme Electrodes," *Phil. Trans. R. Soc. Lond.* B316 :107–119 (1987).

Alcock, S. J. et al., "Continuous Analyte Monitoring to Aid Clinical Practice," *IEEE Engineering in Medicine and Biology*, 319–325 (1994).

Anderson, L. B. et al., "Thin–Layer Electrochemistry: Steady–State Methods of Studying Rate Processes," *J. Elec-*

Bartlett, P. N. et al., "Covalent Binding of Electron Relays to Glucose Oxidation," *J. Chem. Soc. Chem. Commun.*, 1603–1604 (1987).

Bartlett, P. N. et al., "Modification of glucose oxidase by tetrahiafulvalene," *J. Chem. Soc., Chem. Commun.,* 16 (1 page—Abstract only) (1990).

Bartlett, P. N. et al., "Strategies for the Development of Amperometric Enzyme Electrodes," *Biosensors,* 3:359–379 (1987/88).

Bobbioni–Harsch, E. et al., "Lifespan of subcutaneous glucose sensors and their performances during dynamic glycaemia changes in rats," *J. Biomed. Eng.* 15:457–463 (1993).

Brandt, J. et al., "Covalent attachment of proteins to polysaccharide carriers by means of benzoquinone," *Biochim. Biophys. Acta,* 386 (1) (1 page Abstract only) (1975).

Brownlee, M. et al., "A Glucose–Controlled Insulin–Delivery System: Semisynthetic Insulin Bound to Lectin", *Science,* 206(4423):1190–1191 (Dec. 7, 1979).

Cass, A.E.G. et al., "Ferricinum Ion As An Electron Acceptor for Oxido–Reductases," *J. Electroanal. Chem.,* 190 :117–127 (1985).

Cass, A.E.G. et al., "Ferrocine–Mediated Enzyme Electrode for Amperometric Determination of Glucose", *Anal. Chem.,* 56(4):667–671 (Apr. 1984).

Castner, J. F. et al., "Mass Transport and Reaction Kinetic Parameters Determined Electrochemically for Immobilized Glucose Oxidase," *Biochemistry,* 23(10):2203–2210 (1984).

Claremont, D.J. et al., "Biosensors for Continuous In Vivo Glucose Monitoring", *IEEE Engineering in Medicine and Biology Society 10th Annual International Conference*, New Orleans, Louisiana, 3 pgs. (Nov. 4–7, 1988).

Chen, C.Y. et al., "A Biocompatible Needle–Type Glucose Sensor Based on Platinum–Electroplated Carbon Electrode", *Applied Biochemistry and Biotechnology,* 36:211–226 (1992).

Chen, C. Y. et al., "Amperometric Needle–Type Glucose Sensor based on a Modified Platinum Electrode with Diminished Response to Interfering Materials", *Analytica Chimica Acta,* 265:5–14 (1992).

Clark, L.C. et al., "Differential Anodic Enzyme Polarography for the Measurement of Glucose", *Oxygen Transport to Tissue: Instrumentation, Methods, and Physiology*, 127–133 (1973).

Clark, L.C., Jr. et al., "Electrode Systems for Continuous Monitoring in Cardiovascular Surgery," *Annals New York Academy of Sciences*, pp. 29–45 (1962).

Clarke, W. L., et al., "Evaluating Clinical Accuracy of Systems for Self–Monitoring of Blood Glucose," *Diabetes Care,* 10(5):622–628 (Sep.–Oct. 1987).

Csöregi, E. et al., "Design, Characterization, and One–Point in Vivo Calibration of a Subcutaneously Implanted Glucose Electrode," *Anal. Chem.* 66(19):3131–3138 (Oct. 1, 1994).

Csöregi, E. et al., "On–Line Glucose Monitoring by Using Microdialysis Sampling and Amperometric Detection Based on "Wired" Glucose Oxidase in Carbon Paste," *Mikrochim. Acta.* 121:31–40 (1995).

Davis, G., "Electrochemical Techniques for the Development of Amperometric Biosensors", *Biosensors,* 1:161–178 (1985).

Degani, Y. et al., "Direct Electrical Communication between Chemically Modified Enzymes and Metal Electrodes. 1. Electron Transfer from Glucose Oxidase to Metal Electrodes via Electron Relays, Bound Covalently to the Enzyme," *J. Phys. Chem.,* 91(6):1285–1289 (1987).

Degani, Y. et al., "Direct Electrical Communication between Chemically Modified Enzymes and Metal Electrodes. 2. Methods for Bonding Electron–Transfer Relays to Glucose Oxidase and D–Amino–Acid Oxidase," *J. Am. Chem. Soc.,* 110(8):2615–2620 (1988).

Degani, Y. et al., "Electrical Communication between Redox Centers of Glucose Oxidase and Electrodes via Electrostatically and Covalently Bound Redox Polymers," *J. Am. Chem. Soc.,* 111:2357–2358 (1989).

Denisevich, P. et al., "Unidirectional Current Flow and Charge State Trapping at Redox Polymer Interfaces on Bilayer Electrodes: Principles, Experimental Demonstration, and Theory," *J. Am. Chem. Soc.,* 103(16):4727–4737 (1981).

Dicks, J. M., "Ferrocene modified polypyrrole with immobilised glucose oxidase and its application in amperometric glucose microbiosensors," *Ann. Biol. clin.,* 47:607–619 (1989).

Engstrom, R.C., "Electrochemical Pretreatment of Glassy Carbon Electrodes", *Anal. Chem.,* 54(13):2310–2314 (Nov. 1982).

Engstrom, R.C. et al., "Characterization of Electrochemically Pretreated Glassy Carbon Electrodes", *Anal. Chem.,* 56(2):136–141 (Feb. 1984).

Ellis, C. D., "Selectivity and Directed Charge Transfer through an Electroactive Metallopolymer Film," *J. Am. Chem. Soc.,* 103(25):7480–7483 (1981).

Fischer, H. et al., "Intramolecular Electron Transfer Mediated by 4,4'–Bipyridine and Related Bridging Groups", *J. Am. Chem. Soc.,* 98(18):5512–5517 (Sep. 1, 1976).

Foulds, N.C. et al., "Enzyme Entrapment in Electrically Conducting Polymers," *J. Chem. Soc. , Faraday Trans 1.,* 82:1259–1264 (1986).

Foulds, N.C. et al., "Immobilization of Glucose Oxidase in Ferrocene–Modified Pyrrole Polymers," *Anal. Chem.,* 60(22):2473–2478 (Nov. 15, 1988).

Frew, J.E. et al., "Electron–Transfer Biosensors", *Phil. Trans. R. Soc. Lond.,* B316:95–106 (1987).

Gernet, S. et al., "Fabrication and Characterization of a Planar Electrochemical Cell and Its Application as a Glucose Sensor", *Biosensors & Actuators,* 18:59–70 (1989).

Gorton, L. et al., "Selective detection in flow analysis based on the combination of immobilized enzymes and chemically modified electrodes," *Analytica Chimica Acta.,* 250:203–248 (1991).

Gregg, B. A. et al., "Cross–Linked Redox Gels Containing Glucose Oxidase for Amperometric Biosensor Applications," *Analytical Chemistry,* 62(3):258–263 (Feb. 1, 1990).

Gregg, B. A. et al., "Redox Polymer Films Containing Enzymes. 1. A Redox–Conducting Epoxy Cement: Synthesis, Characterization, and Electrocatalytic Oxidation of Hydroquinone," *J. Phys. Chem.,* 95(15):5970–5975 (1991).

Hale, P.D. et al., "A New Class of Amperometric Biosensor Incorporating a Polymeric Electron–Transfer Mediator," *J. Am. Chem. Soc.,* 111(9):3482–3484 (1989).

Harrison, D.J. et al., "Characterization of Perfluorosulfonic Acid Polymer Coated Enzyme Electrodes and a Miniaturized Integrated Potentiostat for Glucose Analysis in Whole

Hawkridge, F. M. et al., "Indirect Coulemetric Titration of Biological Electron Transport Components," *Analytical Chemistry,* 45(7):1021–1027 (Jun. 1973).

Heineman, W.R. et al., "Measurement of Enzyme E°' Values by Optically Transparent Thin Layer Electrochemical Cells", *Analytical Chemistry, 47*(1):79, 82–84 (Jan. 1975).

Heineman, W.R. "Spectro–electro–chemistry", *Analytical Chemistry, 50*(3):390–392, 394, 396, 398, 400, 402 (Mar. 1978).

Heller, A., "Amperometric biosensors based on three–dimensional hydrogel–forming epoxy networks," *Sensors and Actuators B*, 13–14:180–183 (1993).

Heller, A., "Electrical Connection of Enzyme Redox Centers to Electrodes," *J. Phys. Chem.*, 96(9):3579–3587 (1992).

Heller, A., "Electrical Wiring of Redox Enzymes," *Acc. Chem. Res.,* 23(5):129–134 (1990).

Ianniello, R.M. et al. "Immobilized Enzyme Chemically Modified Electrode as an Amperometric Sensor", *Anal. Chem.,* 53(13):2090–2095 (Nov. 1981).

Ianniello, R.M. et al., "Differential Pulse Voltammetric Study of Direct Electron Transfer in Glucose Oxidase Chemically Modified Graphite Electrodes", *Anal. Chem.,* 54:(7):1098–1101 (Jun. 1981).

Ikeda, T. et al., "Glucose oxidase–immobilized benzoquinone–carbon paste electrode as a glucose sensor," *Agric. Biol. Chem.,* 49(2) (1 page—Abstract only) (1985).

Johnson, J. M. et al., "Potential–Dependent Enzymatic Activity in an Enzyme Thin–Layer Cell," *Anal. Chem.* 54:1377–1383 (1982).

Johnson, K. W. et al., "In Vivo Evaulation of an Electroenzymatic Glucose Sensor Implanted in Subcutaneous Tissue", *Biosensors* & bioelectronics 7:709–714 (1992).

Johnson, K.W., "Reproducible Electrodeposition of Biomolecules for the Fabrication of Miniature Electroenzymatic Biosensors", *Sensors and Actuators B Chemical,* B5:85–89 (1991).

Jönsson, G. et al., "An Amperometric Glucose Sensor Made by Modification of a Graphite Electrode Surface With Immobilized Glucose Oxidase and Adsorbed Mediator", *Biosensors,* 1:355–368 (1985).

Josowicz, M. et al., "Electrochemical Pretreatment of Thin Film Platinum Electrodes", *J. Elecrochem. Soc.,* 135(1):112–115 (Jan. 1988).

Katakis, I. et al., "Electrostatic Control of the Electron Transfer Enabling Binding of Recombinant Glucose Oxidase and Redox Polyelectrolytes," *J. Am. Chem. Soc.,* 116(8):3617–3618 (1994).

Katakis, I. et al., "L–α–Glycerophosphate and L–Lactate Electrodes Based on the Electrochemical "Wiring" of Oxidases," *Analytical Chemistry,* 64(9):1008–1013 (May 1, 1992).

Kenausis, G. et al., "'Wiring' of glucose oxidase and lactate oxidase within a hydrogel made with poly(vinyl pyridine) complexed with $[Os(4,4'–dimethoxy–2,2'–bipyridine)_2Cl]^{+/2+}$," *J. Chem. Soc. Faraday Trans.,* 92(20):4131–4136 (1996).

Kondo, T. et al., "A Miniature Glucose Sensor, Implantable in the Blood Stream", *Diabetes Care,* 5(3):218–221 (May–Jun. 1982).

Kulys, J. et al., "Mediatorless peroxidase electrode and preparation of bienzyme sensors," *Bioelectrochemistry and Bioenergetics,* 24:305–311 (1990).

Lager, W. et al., "Implantable Electrocatalytic Glucose Sen-

Lee, J. et al., "A New Glucose Sensor using Microporous Enzyme Membrane", *Sensors and Actuators,* B3:215–219 (1991).

Lewandowski, J.J. et al., "Evaluation of a Miniature Blood Glucose Sensor", *Trans Am Soc Artif Intern Organs,* XXXIV: 255–258 (1988).

Lindner, E. et al. "Flexible (Kapton–Based) Microsensor Arrays of High Stability for Cardiovascular Applications", *J. Chem. Soc.Faraday Trans.,* 89(2):361–367 (Jan. 21, 1993).

Maidan, R. et al., "Elimination of Electrooxidizable Interferant–Produced Currents in Amperometric Biosensors," *Analytical Chemistry, 64*(23):2889–2896 (Dec. 1, 1992).

Mann–Buxbaum, E. et al, "New Microminiaturized Glucose Sensors Using Covalent Immobilization Techniques", *Sensors and Actuators, B1*:518–522 (1990).

Mastrototaro, J.J. et al., "An Electroenzymatic Glucose Sensor Fabricated on a Flexible Substrate", *Sensors and Biosensors B Chemical, B5*:139–144 (1991).

Matthews, D.R. et al., "An Amperometric Needle–Type Glucose Sensor Tested in Rats and Man", *Original Articles,* pp. 248–252 (1988).

McKean et al., "A telemetry–Instrumentation System for Chronically Implanted Glucose and Oxygen Sensors", *IEEE Transactions of Biomedical Engineering,* 35(7):526–532 (Jul. 1988).

McNeil, C. J. et al., "Thermostable Reduced Nicotinamide Adenine Dinucleotide Oxidase: Application to Amperometric Enzyme Assay," *Anal. Chem.,* 61(1):25–29 (Jan. 1, 1989).

Miyawaki, O. et al., "Electrochemical and Glucose Oxidase Coenzyme Activity of Flavin Adenine Dinucleotide Covalently Attached to Glassy Carbon at the Adenine Amino Group", *Biochimica et Biophysica Acta,* 838:60–68 (1985).

Moatti–Sirat, D. et al., "Evaluating in vitro and in vivo the interference of ascorbate and acetaminophen on glucose detection by a needle type glucose sensor," *Biosensors & Bioelectronics,* 7(5):345–352 (1992).

Moatti–Sirat, D. et al., "Reduction of acetaminophen interference in glucose sensors by a composite Nafion membrane: demonstration in rats and man," *Diabetologia,* 37(6) (1 page—Abstract only) (Jun. 1994).

Moatti–Sirat, D. et al., "Towards continuous glucose monitoring: in vivo evaluation of a miniaturized glucose sensor implanted for several days in rat subcutaneous tissue," *Diabetologia,* 35(3) (1 page—Abstract only) (Mar. 1992).

Moser, I. et al., "Advanced Immobilization and Protein Techniques on thin Film Biosensors", *Sensors and Actuators,* B7:356–362 (1992).

Moussy, F. et al., "Performance of Subcutaneously Implanted Needle–Type Glucose Sensors Employing a Novel Trilayer Coating", *Anal. Chem.,* 65:2072–2077 (1993).

Nagy, G. et al., "A New Type of Enzyme Electrode: The Ascorbic Acid Eliminator Electrode," *Life Sciences,* 31(23):2611–2616 (1982).

Nakamura, S. et al., "Effect of Periodate Oxidation on the Structure and Properties of Glucose Oxidase," *Biochimica et Biophysica Acta.,* 445:294–308 (1976).

Narazimhan, K. et al., "p–Benzoquinone activation of metal oxide electrodes for attachment of enzymes," *Enzyme*

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.