

SWORN STATEMENT

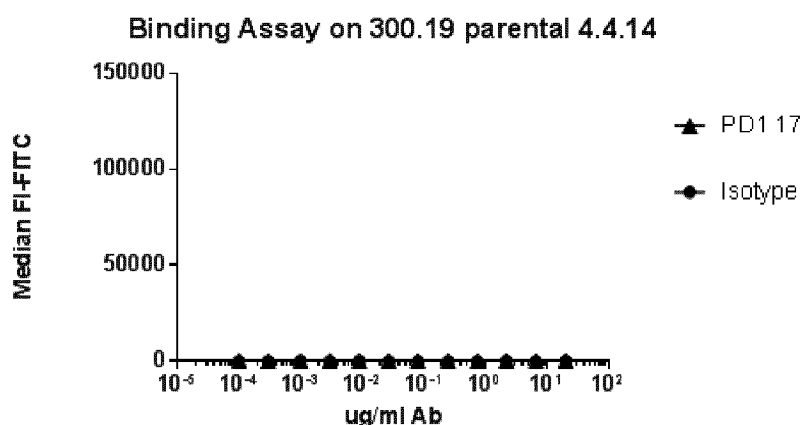
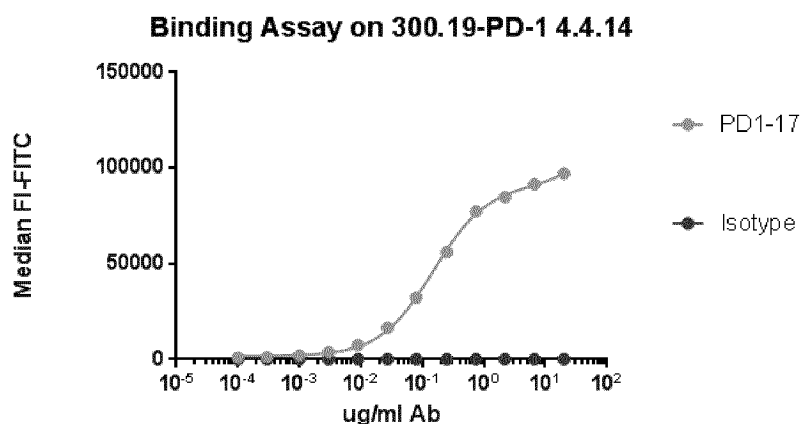
I, Jennifer Mataraza, hereby swear:

1. I am Senior Investigator I at Novartis Institutes of Biomedical Research. I have fourteen years' combined academic and industry experience of target discovery and validation of both small molecule and biologic inhibitors for autoimmune and inflammatory disease, and oncology. My *curriculum vitae* is attached as appendix A.
2. I have been asked by the patent group to oversee various experiments in relation to two antibodies which recognise PD-1 (Programmed Death 1) protein. I understand that the results of these experiments, as reported below, will be used to support an opposition at the European Patent Office against patent EP-2161336 in the names of Ono Pharmaceutical Co., Ltd. and Medarex, Inc.
3. The two test antibodies are human monoclonal IgGs:
 - Monoclonal antibody 5C4. This antibody was synthesized by Aldevron (Madison, WI), by expressing in HEK293 cells the heavy and light chain variable region sequences SEQ ID Nos. 4 and 11 from EP2161336, respectively, as full length human IgG4. The antibody was purified on a Protein A column and analysed by SDS-PAGE for molecular weight, yield and purity.
 - Monoclonal antibody PD1-17. This antibody was synthesized by GenScript (Piscataway, NJ), by expressing in HEK293 cells the heavy and light chain variable region sequences SEQ ID Nos. 4 and 2 from WO2004/056875, respectively, as full length human IgG1. The antibody was purified on a Protein A column and analysed by SDS-PAGE for molecular weight, yield and purity.

Competition Assay: FACS staining on 300.19h cells expressing human PD1

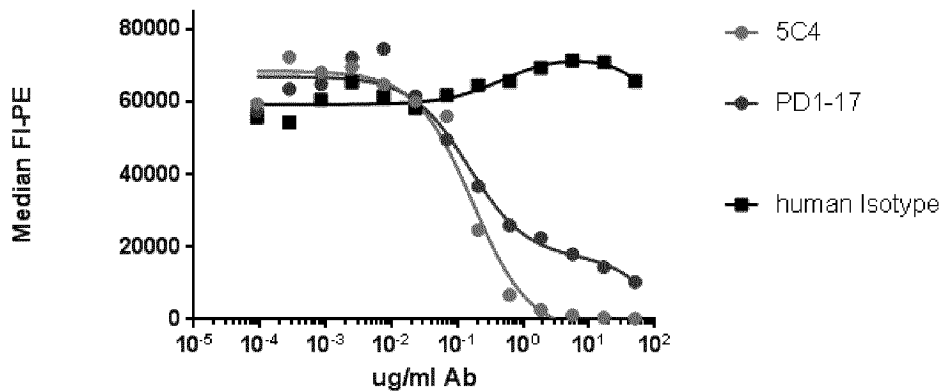
4. I was asked to determine whether the PD1-17 antibody cross-competes for binding to PD-1 with the 5C4 antibody. I assigned this work to a group at Novartis with relevant experience.
5. The assay used the following materials: antibody PD1-17 (5 mg/ml); antibody 5C4 PE-labeled by R-PE lightning link kit from Innova Biosciences (#703-0010) according to the manufacturer's instructions to a final concentration of 0.92 mg/ml; Human isotype IgG4 (1 mg/ml) from Sigma (I4639); murine 300.19 pre-B cells expressing human PD-1 obtained from Professor Gordon Freeman (Harvard Medical School); FACS buffer: 1XPBS, 2% FBS and 2 mM EDTA.

6. All steps were done at 4°C. All buffers were kept cold on ice during the experiment. Centrifugation was done at 4°C. In a 96-well U bottom plate, 5×10^4 cells/well in 50 µl FACS buffer were plated. Unlabelled test anti PD-1 antibodies were titrated serially for 12 points on a 96 well plate (serial 3-fold dilution) starting at 50 µg/ml; 50 µl (3X50 µg/ml working solution) per well added to the cells. 5C4-PE was added immediately (following the addition of unlabelled antibodies) at a fixed concentration (3XKd=3X0.3 µg/ml=0.9 µg/ml), 50 µl per well. Positive control (no antibody added) was included. The plate was incubated at 4°C for 4 hours. 50 µl of FACS buffer was added and cells were spun down at 1500 rpm x 5 min. Supernatants were flicked off. Cells were washed 2X200 µl with FACS buffer-spun down at 1500 rpm x 5 min between washes. Cells were resuspended in 200 µl FACS buffer for acquisition on BD Fortessa. Graphs were prepared by Prism.
7. Firstly, it was confirmed that PD1-17 binds to murine 300.19 pre-B cells stably expressing human PD1 and does not bind to the negative control parental cell line 300.19 that does not express human PD-1:

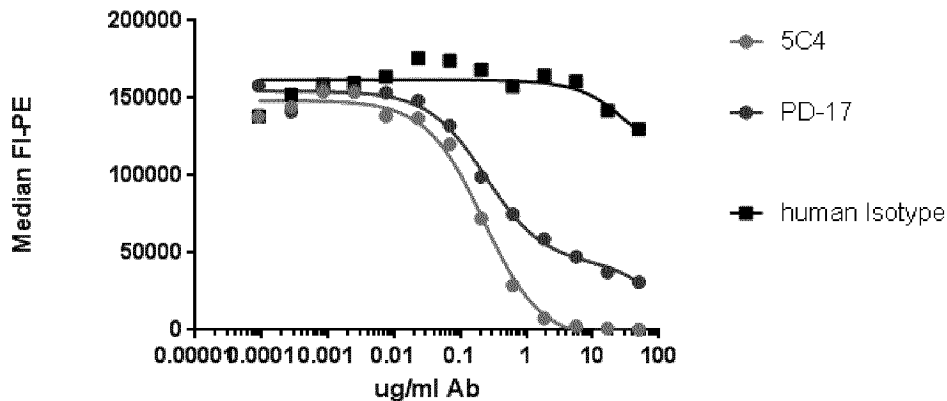


8. Secondly, the PD1-17 antibody was shown in repeat experiments to inhibit the binding of 5C4 to human PD-1 and thereby compete with the 5C4 antibody for binding to the 300.19hPD-1 cells:

Competition PD-1 Abs to 5C4-PE at 0.3 ug/ml 4.3.14



Competition PD-1 Abs to 5C4-PE at 0.3 ug/ml 4.4.14



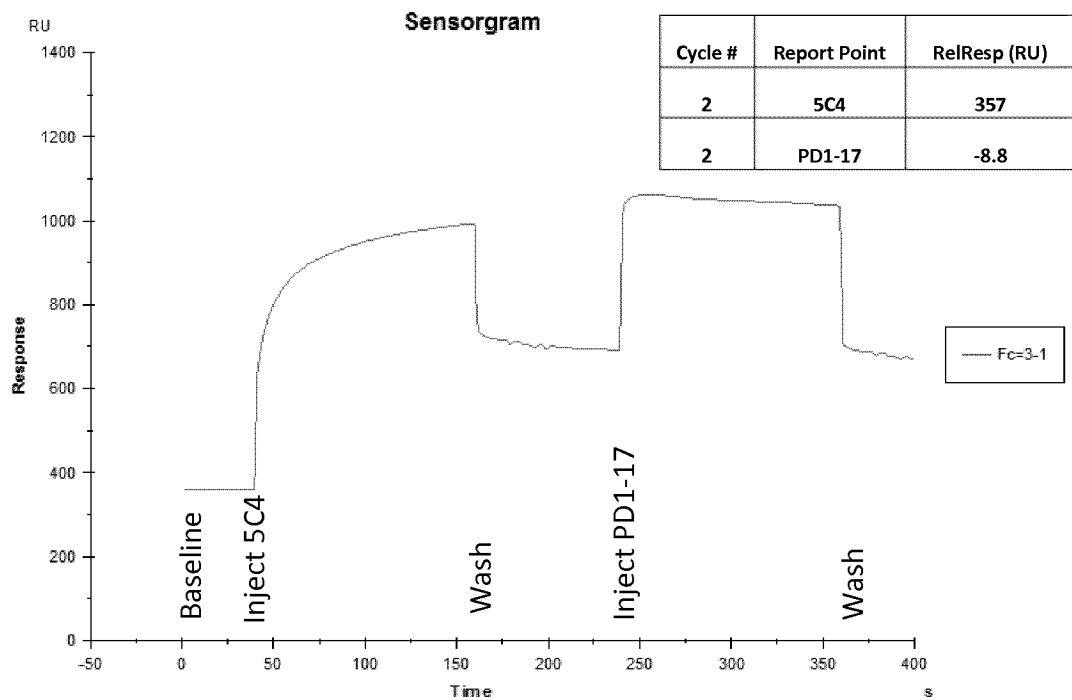
9. These flow cytometry data demonstrate:

- (i) that the human monoclonal PD1-17 antibody binds to murine cells transfected with human PD-1 but not to murine cells that were not transfected with human PD-1; and
- (ii) that the human monoclonal PD1-17 antibody inhibits the binding of the 5C4 antibody to human PD-1, which indicates that PD1-17 competes with 5C4 for binding to human PD-1.

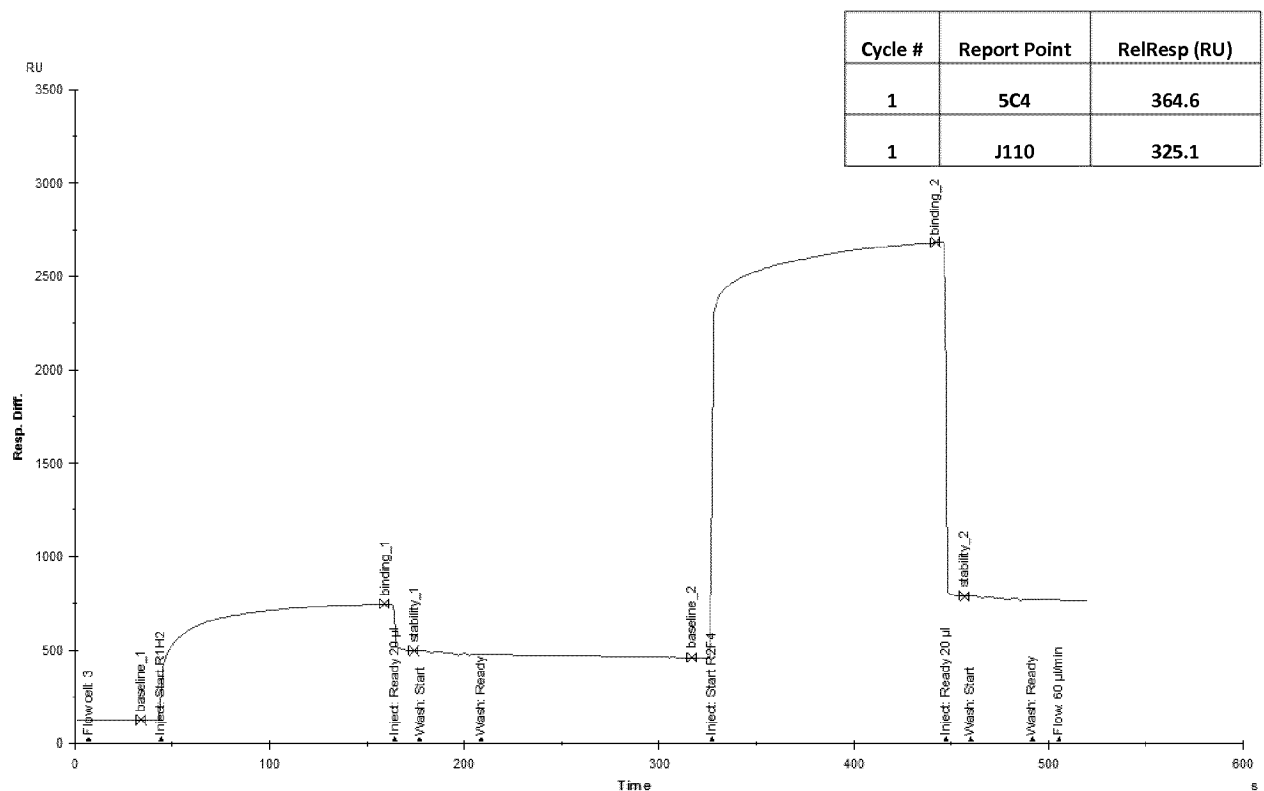
Biacore binding assay

10. I was also asked to assess the binding of the two antibodies to human PD-1 using another standard binding assay. I assigned this work to the Biacore expert group at Novartis. The experiments were performed in a Biacore T100 instrument and a CM5 sensor chip (GE Cat No. BR-1003-99).

11. To confirm that both the 5C4 antibody and the PD1-17 antibody bind to human PD-1 bound to the CM5 sensor chip, human PD-1-Fc obtained from R&D Systems (Cat No. 1086-PD-050) was immobilized at 10µg/ml on the CM5 chip using standard amine chemistry - GE Amine Coupling kit Cat No. BR-1000-50, Acetate pH 5.0 (GE Cat No. BR-1003-51) - at low and high density. The respective test antibody (5C4 or PD1-17) was added at various nanomolar concentrations (0.00; 4.17; 8.34; 16.69; 33.38; 66.75; 133.50; 267.00) through two-fold dilutions in running buffer HBS-EP (GE Cat No. BR-1006-69). Biacore Evaluation software v2.03 was used. The experiment confirmed that both 5C4 and PD1-17 are able to bind to human PD-1 with dissociation constants (K_D) in the nanomolar range. A positive control antibody, J110 (purchased from Lifespan Biosciences, Inc. Cat No. LS-C179390; Data sheet attached as Appendix B), which is known to bind human PD-1, was also shown to bind to human PD-1 with a nanomolar dissociation constant (K_D).
12. To assess whether both antibodies bind to the same epitope on human PD-1, human PD-1-FC obtained from R&D Systems (Cat No. 1086-PD-050) was immobilized at 10µg/ml on the CM5 chip using standard amine chemistry - GE Amine Coupling kit Cat No. BR-1000-50, Acetate pH 5.0 (GE Cat No. BR-1003-51) - at a density of 600RU. Each antibody was diluted in running buffer HBS-EP (GE Cat No. BR-1006-69) at 40µg/ml. The flow rate was set at 10µl/min. The first anti-PD1 antibody (5C4) was injected for two minutes, and a binding curve observed until stabilization - showing that all binding sites of PD-1 are bound to the first antibody (5C4). The chip was then washed with running buffer to remove unbound antibody, and the second anti-PD1 antibody (PD1-17) was injected for two minutes. As a positive control, the same experiment was repeated with an alternative second antibody, J110 (obtained as above) that is known (from page 40 lines 10 to 12 of WO2004/056875) to bind to an epitope on human PD-1 different from the epitope bound by PD1-17. Between experiments, the chip was regenerated using elution buffer from Thermo Scientific Cat No.21027. Biacore Evaluation software v1.1 was used.
13. If there is no response on injection of the second antibody (i.e. the RU value remains the same as after binding of the first antibody), then the first and second antibodies bind to the same epitope. If the second antibody binds to a different epitope from the first antibody, then a positive response (increase in the RU value) should be detected.
14. The result of the 5C4 vs. PD1-17 assay is shown below:



15. This sensorgram shows that the addition of PD1-17, to human PD-1 bound to 5C4, does not produce a positive binding result. The 5C4 antibody therefore inhibits binding of PD1-17 to human PD-1. This means that the 5C4 and PD1-17 compete for the same epitope on human PD-1, because PD1-17 binds to the same epitope on human PD-1 as 5C4.
16. When the second antibody was J110, the sensorgram shows that the addition of the second antibody produces a positive binding result, i.e. that the assay was able to detect the binding of an antibody to a different epitope on human PD-1:



Conclusion

17. Both the flow cytometry and the Biacore data show that PD1-17 cross-competes with 5C4 for binding to human PD-1. The Biacore data show that these two antibodies bind to the same epitope.

I state under penalty of perjury that the above is true.

Signed _____

Executed on _____

4-28-14

DATE

JENNIFER M. MATARAZA

Chestnut Hill Avenue, Brookline, MA

Summary: Ph.D. scientist with fourteen years combined academic and industry experience. Expertise in target discovery and validation of both small molecule and biologic inhibitors for autoimmune and inflammatory disease and oncology. Broad knowledge and research experience in immunology, cell biology, cell cycle, signal transduction and cytokine signaling.

Education:

- Boston College, Chestnut Hill, MA
Ph.D. in Biology, December, 2000.
- Boston College, Chestnut Hill, MA
B.S. *magna cum laude*, in Biology, May, 1994.

Employment History:

- 2/14- Present: Senior Investigator I, Novartis Institutes of Biomedical Research, Cambridge, MA.
- 2/13-2/14: Senior Principal Scientist, CoStim Pharmaceuticals, Cambridge MA.
(Acquired by Novartis)
 - Project team leadership for humanized mAb programs directed at immune checkpoint inhibitors for oncology indications
 - Hands-on and supervised immune cell assay development and optimization
 - Academic and CRO collaboration management
 - Responsible for lab setup and biosafety management
 - Managed team of two junior PhD scientists
- 12/12-4/13: Adjunct Faculty, Biology, Massachusetts College of Pharmacy and Health Sciences, Boston, MA.
 - Instructor for Introductory Biology laboratories
- 11/10-11/12: Respiratory and Immunology Team Member, Merck Research Laboratories, Boston, MA.
 - Member of several program core teams- expertise in *in vitro* immune cell assay development for small molecule target discovery and validation
 - Presented at project team meetings as a department representative
 - Scientific management of research associates and interns
 - Managed outsourced collaborative projects with multiple CROs
 - Researched and presented new target validation proposals
 - Member of Immunotoxicology Advisory Council
 - Infection liability assessment for all department program teams
 - Assay development for oncology and metabolic disease core teams
- 11/07-11/10: Associate Principal Scientist, Schering Plough Research Institute, Cambridge, MA. (Acquired by Merck)
8/05-11/07: Scientist II, Organon Biosciences, Cambridge, MA. (Acquired by Schering-Plough)
 - Program team lead for biologics target discovery and validation for monoclonal antibody therapeutics

- Directed professional staff of 1-3 research associates and/or interns
 - Managed both industrial and academic collaborations
 - Published technical reports internally
- 8/03-8/05: Research Assistant Professor, Department of Biology, Boston College, Chestnut Hill, MA.
 - Taught graduate level lecture course in Immunology
 - Established collaborative project in nanotechnology with Physics department
 - Managed graduate and undergraduate student research projects investigating kinase signaling and glucose metabolism in mouse B cells
- 9/01-8/03: Part-Time Faculty – Molecular and Cellular Biology and Genetics Laboratory, Department of Biology, Boston College, Chestnut Hill, MA.
 - Mentored undergraduate students in scientific writing skills and laboratory report writing
- 10/00-8/03: Postdoctoral Fellow, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA. (mentor: Dr. David B. Sacks)
 - Studied signaling pathways associated with the scaffolding protein IQGAP1
- 9/96–10/00: Graduate Student, Department of Biology, Boston College, Chestnut Hill, MA. (mentor: Dr. Thomas C. Chiles)
 - Studied MAPK kinase signaling and apoptosis in murine B cells
- 6/94-7/96: Research Assistant, New England Deaconess Hospital and Harvard Medical School, Boston, MA.
 - Studied cadherin expression in bladder carcinoma cell lines

Technical Expertise:

- Primary cell isolation/culture (rodent, non-human primate and human), flow cytometry, confocal microscopy, ELISA, ELISpot, various immune cell *in vitro* functional assays (T cell, B cell, dendritic cell, neutrophil, macrophage/monocyte, NK cell), immunotoxicology assessment, qPCR, apoptosis assays, Western blotting, kinase/reporter gene/apoptosis assays, tissue sectioning and immunohistochemistry, mouse/rat husbandry/basic surgery, cloning, transfection, stable cell line development.

Grants and Awards:

- National Research Service Award Institutional Grant, PHS # 5 T32 HL07627-16, 10/00-8/03.
- ASBMB Postdoctoral Travel Award, April, 2002.
- Michael P. Walsh Fellowship Recipient, 1998 - 1999, 1999 - 2000.
- Donald J. White Teaching Excellence Award, Boston College 1998.
- Scholar of the College, Boston College, May 1994.

Patents:

- **Mataraza J.M.**, Van Elsas, A., Korman, A., Halk, E.L., Thudium, K.B., Selby, M., Sproul, T.W., and Leblanc, H.N. "Fully Human Antibodies to BTLA." Patent WO 2011014438 A1.

Publications:

- Jadeski, L.*, **Mataraza, J.M.***, Li, Z., Jeong, H-W. and D.B. Sacks (2008) IQGAP1 Stimulates Proliferation and Enhances Tumorigenesis of Human Breast Epithelial Cells. *Journal of Biological Chemistry* 283:1008-17.
- **Mataraza, J.M.**, Li, Z., Jeong, H-W., Brown, M.D. and D.B Sacks. (2007) Multiple Proteins Mediate IQGAP1-Stimulated Cell Migration. *Cellular Signaling* 19:1857-65.
- **Mataraza, J.M.**, Tumang J., Gumina M.R, Gurdak S.M., Rothstein T.L., and T.C. Chiles (2006) Disruption of Cyclin D3 Blocks Proliferation of Normal B-1a Cells, but Loss of Cyclin D3 is Compensated by Cyclin D2 in Cyclin D3-Deficient Mice. *Journal of Immunology* 15:787-95.
- Doughty, C.A., Bleiman, B.F., Wagner, D.J., Dufort, F.J., **Mataraza, J.M.**, Roberts, M.F., and T. C. Chiles (2006) Antigen Receptor-mediated Changes in Glucose Metabolism in B Lymphocytes: Role of Phosphatidylinositol 3-kinase Signaling in the Glycolytic Control of Growth. *Blood* 107:4458-65.
- Cai, D., **Mataraza, J.M.**, Huang, Z., Huang, J., Qin, Z., Chiles, T.C., Carnahan, D., Kempa, K. and Z.F. Ren. (2005) Highly Efficient Molecular Delivery into Mammalian Cells Using Carbon Nanotube Spearing. *Nature Methods* 2:449-454.
- Blois, J.T., **Mataraza, J.M.**, Mecklenbrauker, I., Tarakhovsky, A., and T.C. Chiles. (2004) B Cell Receptor-induced cAMP-response Element Binding Protein Activation in B Lymphocytes Requires Novel Protein Kinase C δ . *Journal of Biological Chemistry* 279:30123-32.
- Cifuentes, E., **Mataraza, J.M.**, Yoshida, B.A., Menon, M., Sacks, D.B., Barrack, E., and P.V.G. Reddy. (2004) Physical and Functional Interaction of Androgen Receptor with Calmodulin in Prostate Cancer Cells. *Proceedings of the National Academy of Sciences* 101:464-469.
- **Mataraza, J.M.**, Briggs, M.W., Li, Z., Entwistle, A., Ridley, A., and D.B. Sacks (2003) IQGAP1 Promotes Cell Motility and Invasion. *Journal of Biological Chemistry* 278:41237-45.
- **Mataraza, J.M.**, Briggs, M.W., Li, Z., Frank, R., and D.B. Sacks (2003) Identification and Characterization of the Cdc42-Binding Site of IQGAP1. *Biochemical and Biophysical Research Communications* 305:315-321.
- **Swart-Mataraza, J.M.**, Li, Z., and D.B. Sacks (2002) IQGAP1 Mediates Active Cdc42 Signaling to the Cytoskeleton. *Journal of Biological Chemistry* 277:24753-24763.
- **Swart, J.M.**, and T.C. Chiles (2000) Rescue of CH31 B-Cells from Antigen Receptor-Induced Apoptosis by Inhibition of p38 MAPK. *Biochemical and Biophysical Research Communications* 276:417-421.
- **Swart, J.M.**, Bergeron, D.M. and T.C. Chiles (2000) Identification of a Membrane Ig-Induced p38 MAPK Module that Regulates cAMP Response Element (CRE)-Binding Protein Phosphorylation and Transcriptional Activation in CH31 B-Cell Lymphomas. *Journal of Immunology* 164:2311-2319.
- Amato, S.F*., **Swart, J.M*.**, Berg, M., Wanebo, H.J., Mehta, S.R and T.C. Chiles (1998) Transient Stimulation of the c-Jun NH₂ Terminal Kinase/Activator Protein 1 Pathway and

Inhibition of Extracellular Signal-Regulated Kinase are Early Effects in Paclitaxel-Mediated Apoptosis in Human B Lymphoblasts. *Cancer Research* 58:241-247.

- Rieger, K.M., Little, A.F., **Swart, J.M.**, Kastrinakis, W.V., Fitzgerald, J.M., Hess, D.T., Libertino, J.A. and I.C. Summerhayes (1995) Human Bladder Carcinoma Cell Lines as Indicators of Oncogenic Change Relevant to Urothelial Neoplastic Progression. *British Journal of Cancer* 72:683-690.

(* co-first author)

Select Scientific Poster Presentations and Seminars:

- **Mataraza, J.M.**, Tumang, J., Gumina, M., Gurdak, S.M., Rothstein, T.L. and T. C. Chiles. Disruption of cyclin D3 blocks proliferation and B-1a cells but loss of cyclin D3 is compensated by cyclin D2 in mutant animals. Immunology 2006 Meeting, Boston, MA, May 2006.
- **Mataraza, J.M.**. The Role of IQGAP1 in Regulating Cdc42 Signaling to the Cytoskeleton and Cell Motility. Boston University School of Medicine, Hematology/Oncology Research Roundtable. January 8, 2004. Invited Speaker.
- **Mataraza, J.M.**, Briggs, M.W., Li, Z., Entwistle, A., Ridley, A., and D.B. Sacks. IQGAP1 promotes cell motility and invasion. Gordon Research Conference: Mechanisms of Cell Signaling, Ventura, CA, June 2003.
- **Mataraza, J.M.**, Li, Z. and D.B. Sacks. IQGAP1 Mediates Active Cdc42 Signaling to the Cytoskeleton. Experimental Biology 2002, New Orleans, LA, April 2002. *FASEB J* 16(4):A170.
- **Swart, J.M.**, Bergeron, D. and T.C. Chiles. B-Cell Antigen Receptor-Induced cAMP Response Element-Binding Protein (CREB) Activation Requires p38 MAPK in CH31 and WEHI-231 B-Cell Lymphomas. Immunology 2000 Meeting, Seattle, WA, May 2000. *FASEB J* 14(6):A968.

Teaching Experience:

- | | |
|-------------------------|--|
| • Spring 2005 | BI540 Immunology. Undergraduate/Graduate Lecture course. |
| • Fall 2001-Spring 2004 | BI310/311 Molecular Cell Biology and Genetics Laboratory. |
| • Fall 1997/Spring 1998 | BI304/305 Molecular Cell Biology and Genetics. Lecture teaching assistant. |
| • Fall 1996/Spring 1997 | Introductory Biology Laboratory. Laboratory teaching assistant. |
| • 1994-2005 | Biology Tutor for High School Science students |

Professional Societies/Volunteer Work:

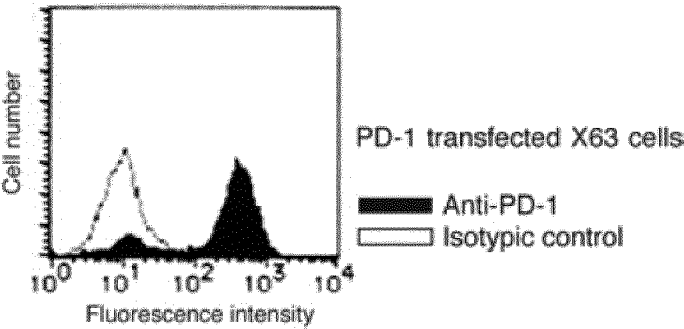
- AAI (American Association of Immunologists)
- The Council for Women of Boston College, Associate Member
- Boston College Connections Mentor Program



PDCD1 / CD279 / PD-1 Mouse anti-Human Monoclonal (J110) Antibody - LS-C179390 - LSBio	
CatalogID:	LS-C179390
Target:	programmed cell death 1 (PDCD1)
Synonyms:	PDCD1 Antibody, CD279 Antibody, HPD-1 Antibody, HPD-I Antibody, PD1 Antibody, Protein PD-1 Antibody, SLEB2 Antibody, PD-1 Antibody, CD279 antigen Antibody, Programmed cell death 1 Antibody
Family / Subfamily:	Apoptosis
Host	PDCD1 antibody was produced in Mouse
Clonality:	Monoclonal
Isotype:	IgG1
Clone Name:	J110
Immunogen Species:	PDCD1 / CD279 / PD-1 antibody was raised against Human
Antigen Type:	Fusion protein
Immunogen:	PDCD1 / CD279 / PD-1 antibody was raised against fc-fusion human PD-1 protein.
Specificity:	human CD279 / PD-1
Reactivity:	Human
Purification:	Protein A purified
Presentation:	PBS, pH 7.2, 50% glycerol
Recommended Storage:	Store at -20°C.
Uses:	Western blot (1 µg/ml), Flow Cytometry (Optimal dilution to be determined by the researcher)
Size:	100 µg
Concentration:	1 mg/ml

Flow Cytometry Image:

■ Flow Cytometry



Requested From: United States

Laboratory Reagent For In Vitro Research Use Only

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