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14. ABSTRACT Disease persistence is the main issue faced by CML patients on therapy with imatinib and eradication of persistent malignant cells will be critical for the long-term success of kinase inhibitor therapy. Mechanisms underlying acquired resistance to imatinib have been extensively studied and the manner by which mutations of the Bcr-Abl kinase domain can reduce or eliminate sensitivity of CML cells to imatinib has been well characterized. Disease persistence in responding patients, in contrast, is still poorly understood. We sought to identify and extensively characterize hematopoietic stem cells responsible for disease persistence and explore their mechanisms of imatinib resistance. Using in vitro culture of primary CML progenitor cells, we identified both quiescent and cycling cells capable of surviving in the presence of imatinib. We observed inhibition of tyrosine phosphorylation by imatinib in surviving cells, suggesting a Bcr-Abl independent mechanism of survival. To apply information gained from in vitro culture to persistent cell populations in treated CML patients, we attempted to isolate Bcr-Abl positive cells from patients in cytogenetic remission. Although persistent CML cells may reside within the stem cell compartment, techniques of stem cell enrichment did not lead to enrichment of CML cells. We are therefore developing techniques for Bcr-Abl-specific detection to facilitate these studies, including creation of a Bcr-Abl junction-specific antibody, development of a Bcr-Abl mRNA junction-specific molecular beacon and analysis of potential markers of CML cells. Evaluation of the utility of these techniques in primary cells is ongoing. The detailed analysis of primary samples is technically challenging, but is essential for an understanding of disease persistence and may allow identification of novel drug targets or methods to sensitize resistant cells to imatinib or alternative Bcr-Abl kinase inhibitors.					
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INTRODUCTION

Targeted therapy with the Abl kinase inhibitor imatinib (Gleevec) induces hematologic and cytogenetic remission in the majority of chronic phase CML¹. Very few patients, however, have undetectable leukemic cells when more sensitive detection techniques are used and the majority of these patients relapse if imatinib is discontinued². Thus, disease persistence is the main issue faced by the majority of CML patients on therapy with imatinib and eradication of persistent malignant cells will be critical for the long-term success of kinase inhibitor therapy. As Bcr-Abl positive cells persist for up to five years, thus far, this argues that some imatinib-resistant populations are hematopoietic stem cells (HSC) with long-term self-renewal capacity. In fact, CD34⁺ cells from complete cytogenetic remission (CCR) patients are enriched for Bcr-Abl⁺ cells³. Many mechanisms of disease persistence have been proposed, including drug efflux⁴⁻⁸, Bcr-Abl kinase domain mutations⁹, Bcr-Abl amplification¹⁰, stem cell quiescence^{11,12} and protection by the bone marrow microenvironment¹³. Evidence that these processes apply to persistent cells is limited and mostly circumstantial and thorough analysis of resistance mechanisms in persistent cells from CCR patients has not been done. The goals of this project are to identify and extensively characterize hematopoietic stem cells responsible for disease persistence and explore their mechanisms of imatinib resistance.

The specific aims are: 1) To determine if Bcr-Abl is active in HSC populations that survive imatinib treatment and to determine which mechanisms contribute to the survival of these cells; and 2) To determine which subpopulations of cells are persistently Bcr-Abl⁺ in imatinib treated CML patients that have achieved CCR.

BODY

Aim 1 – Determine if Bcr-Abl is active in HSC populations that survive imatinib treatment and to determine which mechanisms contribute to the survival of these cells

In vitro culture of CML stem cells with imatinib

Initially, we wished to determine whether Bcr-Abl is active in primary CML cells that survive culture in imatinib. For these studies, bone marrow and leukapheresis samples from seven newly diagnosed, imatinib-naïve chronic phase CML patients and two normal samples were used. Mononuclear cells, isolated by Ficoll centrifugation, were depleted, by immunomagnetic separation, of cells expressing lineage markers. Lin⁻ cells were cultured in serum free medium either without cytokines or with a five cytokine cocktail (100ng/mL Flt ligand, 100ng/mL SCF, 20ng/mL IL-3, 20ng/mL IL-6, 20ng/mL G-CSF) in the presence of imatinib for four days as described¹². Initial experiments were done in the absence of cytokines, a culture condition that supports the growth of primitive Bcr-Abl⁺ but not normal cells¹⁴; however, we found by culturing normal samples that a fraction of normal bone marrow Lin⁻ cells were capable of surviving in these culture conditions (Table 1). Additional experiments were therefore done in the presence of cytokines to more closely represent native conditions. Results observed in both culture conditions are presented here. Cell density was monitored daily to determine the degree of cell expansion. Both in the absence and presence of cytokines, Ph⁺ cells were able to survive imatinib treatment (Tables 1,2).

Table 1. Cell growth, phenotype and cell cycle status of primary CML cells and normal bone marrow cultured in the presence or absence of imatinib (IM).

Sample	Culture Condition	Fold Cell Expansion	Ph ⁺
CML1	No Drug	1.6	95%
	Imatinib	0.14	9%
CML2	No Drug	2.7	Nd
	Imatinib	0.94	Nd
CML3	No Drug	2.1	96%
	Imatinib	0.4	93%
CML4	No Drug	0.5	98%
	Imatinib	0.57	97%
normal1	No Drug	0.44	0%
	Imatinib	0.34	0%
normal2	No Drug	0.2	0%
	Imatinib	0.28	0%

Additionally, in the presence of cytokines, all samples showed a net expansion of cells treated with imatinib and similar cell cycle status as their untreated counterparts (Table 2), indicating the capacity to proliferate in the presence of the inhibitor. Acridine Orange staining demonstrated a slight increase in the G₀ fraction with imatinib treatment in all samples; however, this only represented 17-31% of cells. This suggests that there are mechanisms of cell survival in addition to quiescence, as previously reported¹². Cells were analyzed for expression of lineage specific markers and stem cell markers. Prior to culture, all samples were >90% Lin⁻ (not shown). Following culture there was an increase in expression of lineage markers and a decrease in CD34 expression. There was a greater decrease in Lin⁻, CD34⁺ and CD133⁺ cells, in imatinib treated cultures indicating enhanced cell differentiation during the culture period (Table 2). This may be due to inhibition of Kit by imatinib, as we have observed in additional experiments that culture with SCF maintains an immature phenotype of primary CML cells (not shown).

Table 2. Cell growth, phenotype and cell cycle status of primary CML cells cultured in the presence or absence of imatinib (IM) in a five-cytokine cocktail.

Sample	Culture	Fold Cell expansion	Ph ⁺	Lin ⁻	CD34 ⁺	CD133 ⁺	G ₀ / G ₁	G ₀
CML5	-IM	4	97%	58%	59%	9%	75%	12%
	+IM	2.6	94%	41%	41%	5%	78%	17%
CML6	-IM	15	99%	55%	48%	10%	61%	4%
	+IM	4.9	99%	39%	42%	7%	67%	10%
CML7	-IM	9.5	100%	81%	83%	70%	75%	26%
	+IM	2.8	97%	75%	67%	56%	68%	31%

CML cells surviving imatinib treatment were analyzed for inhibition of Bcr-Abl activity. When sufficient cell numbers were available, this was done by western blotting for phosphotyrosine in untreated and treated cell lysates. Intracellular FACS for Bcr-Abl-specific targets P-CrkL, P-Abl and total P-tyr was explored as a means of analyzing small numbers of primary cells. In CD34⁺ CML cells all three antibodies demonstrated target specificity; however, total phosphotyrosine was chosen for our studies based on superior signal relative to background (Figure 1).

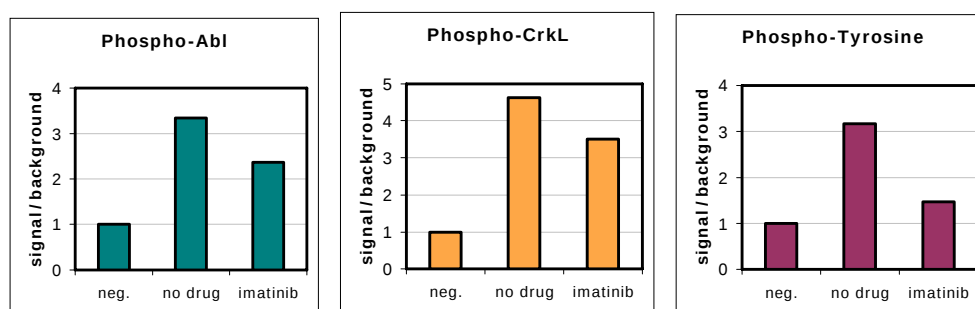


Figure 1. Intracellular FACS analysis of CML CD34⁺ cells using phospho-Abl (left), phospho-CrkL (middle) and total phosphotyrosine (right) antibodies. Signal relative to background is shown for cells incubated with or without 10 μM imatinib.

Imatinib treated cells showed a dramatic inhibition of cellular phosphotyrosine levels (Figure 2A). This could be at least partially reversed by washing imatinib from the culture. Representative western blot and intracellular P-FACS are shown (Figure 2B,C). It is unclear whether incomplete restoration of phosphorylation upon washout is due to an overall decrease in Bcr-Abl activity in imatinib treated cells, or incomplete removal of drug. These results indicate that a fraction of CML progenitors can survive and proliferate in conditions that inhibit Bcr-Abl kinase activity. These results must, however, be interpreted cautiously. Increased expression of lineage-specific markers and decreased expression of stem cell markers during the culture period indicate that the initial population and the final population are phenotypically different. It is therefore unclear whether the initial population would likewise demonstrate Bcr-Abl inhibition or whether the cells we observed at the end of the culture period were differentiated to a point where they had become imatinib sensitive. As apoptotic effects of imatinib in cell lines require several days in culture¹⁵, it is not feasible to shorten the culture period, thus *in vitro* culture studies are limited in their ability to provide information about persistent populations.

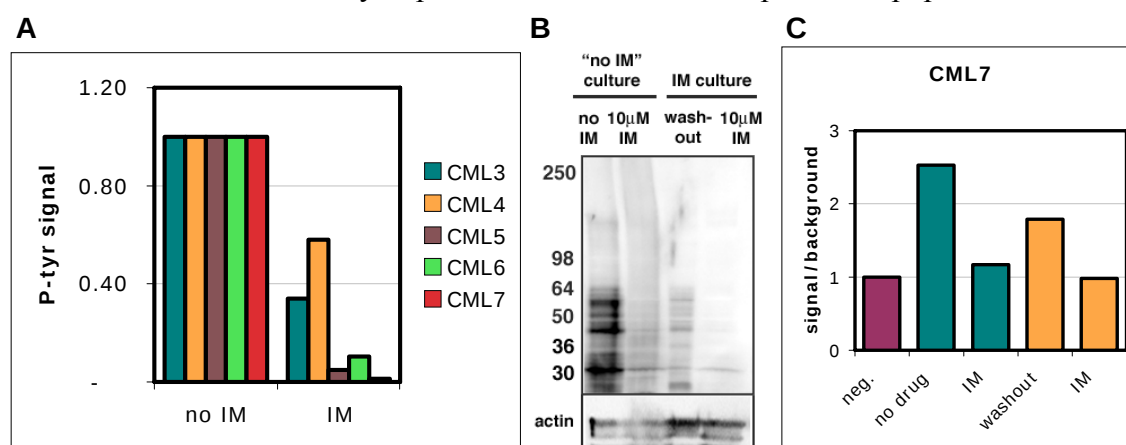


Figure 2. Inhibition of phosphotyrosine in CML Lin- cells cultured with 10mM imatinib. **A)** composite data from western blots and phospho-FACS is shown for five CML samples. **B)** Representative western blot of cells cultured with “no drug” with or without a short incubation of imatinib and cells cultured with imatinib in which imatinib was either left in prior to lysis, or washed out. **C)** Representative phospho-FACS analysis of conditions described for panel B.

Aim 2 – Determine which subpopulations of cells are persistently Bcr-Abl⁺ in imatinib treated CML patients that have achieved CCR

Seeking persistent cells using stem cell enrichment techniques

Because of challenges interpreting *in vitro* culture results, we chose to focus our study on persistent cells in patients who had achieved a complete cytogenetic remission without a molecular remission. Initially, we determined whether enriching stem/progenitor cells would also enrich residual Ph⁺ cells as was previously suggested³. Bone marrow from CCR patients was lineage depleted and FACS sorted into CD34⁺CD38⁻, CD34⁺CD38^{low}, CD34⁺CD38⁺ and Lin⁺ fractions and analyzed by FISH for the presence of Bcr-Abl. In two samples, 1% Ph⁺ cells were seen in the CD34⁺CD38^{low} fraction (Table 3), however, this was not sufficient enrichment to pursue this method.

Table 3. Analysis of Bcr-Abl⁺ cells in stem/progenitor cell fractions of CCR patients.

sample ID	34 ⁺ 38 ⁻ % Ph ⁺	34 ⁺ 38 ^{low} % Ph ⁺	34 ⁺ 38 ⁺ % Ph ⁺	Lin ⁺ % Ph ⁺
CCR1	0	-	0	-
CCR2	0	1	0	0
CCR3	0	1	0	0
CCR4	0	0	0	0

Because our study and previous studies demonstrated survival and accumulation of primitive quiescent Bcr-Abl⁺ cells in the presence of imatinib¹², we additionally analyzed Lin⁻G₀ cells from CCR patients. No enrichment of Bcr-Abl⁺ cells was observed in the primitive quiescent fraction (Table 4). We concluded that methods of stem cell isolation were unlikely to enrich Bcr-Abl positive cells sufficiently for our studies.

Enrichment of Bcr-Abl-expressing cells

We next sought to refine our methods of Bcr-Abl⁺ cell enrichment by developing Bcr-Abl-specific means of cell separation. We simultaneously initiated multiple approaches, including detection of Bcr-Abl protein, detection of Bcr-Abl mRNA and identification of CML progenitor cell-specific markers.

Table 4. Analysis of Bcr-Abl⁺ cells in quiescent stem/progenitor cells of CCR patients.

sample ID	% G ₀	% Ph ⁺ G ₀	% Ph ⁺ “not G ₀ ”
CCR5	65	0	0
CCR6	31	5.7	5.9
CCR7	22	0	0
CCR8	53	0	0
CCR9	60	5.4	0
CCR10	46	0	0

Bcr-Abl junction-specific antibodies

To detect Bcr-Abl protein independently of c-Bcr and c-Abl, we generated antibodies in chickens (Aves Laboratory) specific to the Bcr-Abl junction regions b3a2 and b2a2¹⁶. Antibody target recognition was validated by immunoprecipitation (Figure 3A) and flow cytometry (Figure 3B). The b3a2 antibody was capable of immunoprecipitating Bcr-Abl and demonstrated a statistically significant increase in fluorescence signal by FACS in Bcr-Abl b3a2-expressing cells relative to Bcr-Abl negative and Bcr-Abl b2a2 expressing cells. Specificity was not seen with the b2a2 antibody.

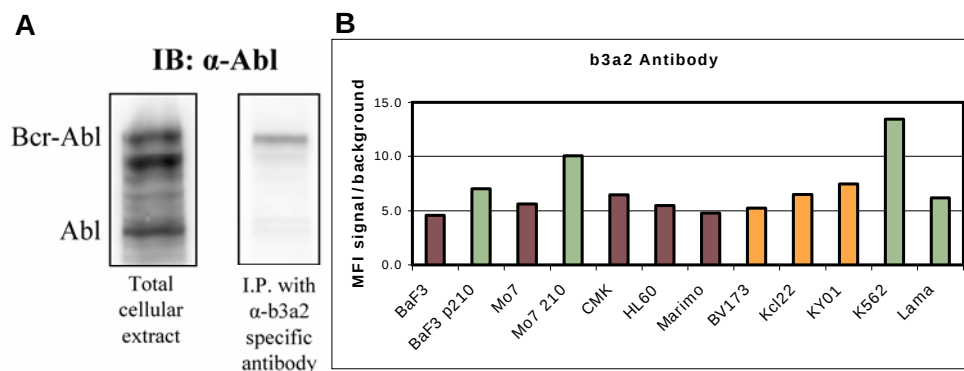


Figure 3. Detection of Bcr-Abl using a b3a2 junction-specific antibody. **A)** Immunoprecipitation of Bcr-Abl with a b3a2 antibody. **B)** Intracellular FACS with a b3a2 antibody in Bcr-Abl negative (purple) b3a2 (green) and b2a2 (orange) Bcr-Abl expressing cells.

K562 cells diluted into Bcr-Abl-negative HL60 cells were sorted based on the b3a2 antibody signal and sorted populations were analyzed by FISH for Bcr-Abl. Enrichment of Bcr-Abl⁺ cells was seen even in a high background of Bcr-Abl⁻ cells (Table 5).

Table 5. Enrichment of Bcr-Abl⁺ cells with a Bcr-Abl b3a2-specific antibody

Dilution	Post Sort b3a2 ⁻ % Ph ⁺	Post Sort b3a2 ⁺ % Ph ⁺
1:1 K562:HL60	1%	100%
1:100 K562:HL60	0%	72%

CML CD34⁺ and normal CD34⁺ bone marrow cells were analyzed by intracellular FACS with the b3a2 antibody. Selective detection of CML cells was observed (Figure 4).

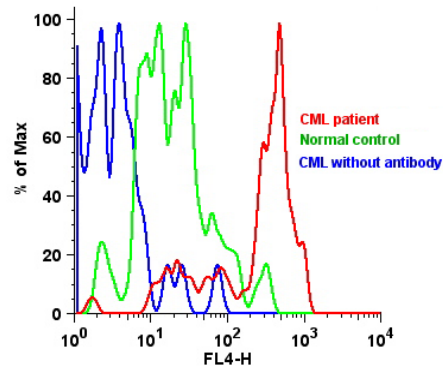


Figure 4. Intracellular FACS analysis of normal (green) and CML (red) CD34⁺ cells with a b3a2 specific Bcr-Abl antibody.

Future experiments include increasing the number of primary specimens used to test the b3a2 antibody and FACS sorting CML CD34⁺ cells diluted into a normal background to test the utility of this antibody for selection of CML cells. Because this is a polyclonal antibody, high background staining may obscure weaker differences in signal. To address this issue, we will employ methods of subtractive affinity purification to remove any contaminating antibodies that may bind to c-Bcr or c-Abl. Once specific recognition is reproducibly established, CCR CD34⁺ cells will be FACS sorted based on b3a2 signal and analyzed for enrichment of Bcr-Abl⁺ cells.

Bcr-Abl mRNA hybridization

To specifically detect Bcr-Abl mRNA, we designed a single stranded DNA probe against the Bcr-Abl b3a2 junction. A molecular beacon dye/quencher strategy was used as a method of signal detection¹⁷. Bcr-Abl specific signal was observed in K562 cells with the molecular beacon relative to a non-specific scrambled probe (Figure 5) however background signal was high, even under optimized hybridization conditions. Addition of a second probe to introduce a dual FRET molecular beacon strategy has been shown to reduce non-specific background¹⁷.

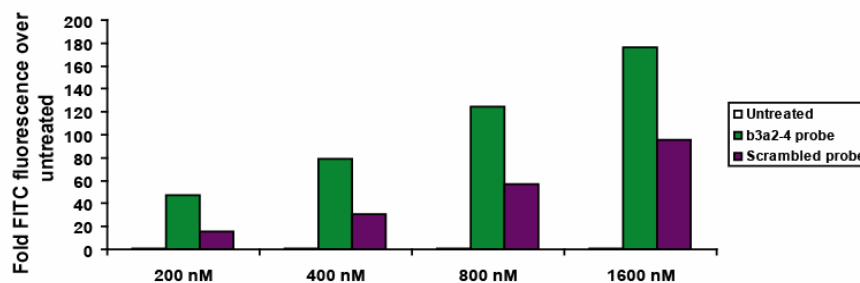


Figure 5. Detection of Bcr-Abl in K562 using a b3a2 junction-specific molecular beacon (green) versus a non-specific scrambled probe (purple).

CML-specific markers

An alternative strategy to isolate CML cells from a normal background is to identify markers that are specific for CML stem and progenitor cells. Literature searches identified CD33^{18,19}, CD123^{19,20} and WT-1²¹ as candidate markers that were shown to be upregulated either at the mRNA or protein level in CML versus normal cells. Additionally, we performed a microarray

meta-analysis using publicly available data of gene expression profiles in normal versus CML CD34⁺ cells²² as well as CML CD34⁺ data that we generated in the context of a separate project. Several candidate cell-surface as well as intracellular markers were identified (Table 6).

Table 6. FACS analysis of candidate markers for CML and normal stem/progenitor cells.

gene	mRNA CML / normal	FACS CML / normal	p value
Leptin Receptor	3.9	1.5	0.14
CD29	3.1	1.1	0.23
CD114	0.30	1.3	0.19
CD61	0.23	1.6	0.14
CD54*	0.20	1.3	0.004
CD33	n/a	2.7	0.12
CD123	n/a	1.0	0.50
Prefoldin-4*	10.1	1.5	0.007
Ski*	9.2	1.4	0.03
K-Ras*	6.7	1.3	0.04
RALA	5.4	1.1	0.13
Opioid receptor mu1	4.4	1.1	0.36
Jak2	4.3	1.2	0.14
TRF1	4.3	1.5	0.06
WT-1*	n/a	1.3	0.008
c-Abl/Bcr-Abl*	n/a	1.6	0.00007
c-Bcr/Bcr-Abl	n/a	1.0	0.38

Abl and Bcr expression levels relative to Bcr-Abl were also considered. All candidate markers were analyzed by FACS using cell surface or intracellular staining of CML and normal CD34⁺ cells. Relative fluorescence intensities of CML/normal were compared (table 6). Representative data for WT-1 is shown (Figure 6).

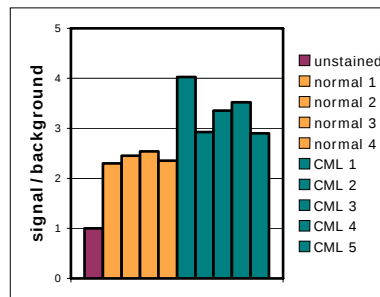


Figure 6. Intracellular FACS analysis of WT-1 expression in normal (orange) and CML (teal) CD34⁺ cells.

Those demonstrating a statistically different signal between normal and CML (represented by *) all showed <2-fold difference in CML/normal. Additional optimization steps were taken to determine whether the CML-specific signal could be enhanced. Among the difficulties encountered were limited availability of suitable monoclonal antibodies, poor antibody quality,

poor antibody specificity and the need to optimize cell permeabilization techniques for intracellular staining. Western blots of a variety of Bcr-Abl negative and positive cell lines demonstrated that the antibody for prefoldin 4 was unable to recognize its target and available antibodies for K-Ras recognize all of the Ras isoforms. Thus, these targets were discarded. Ski-1 and TRF-1 antibodies both showed specificity for their targets in western blots and by FACS analysis, however, the optimal permeabilization technique for FACS was incompatible with cell surface staining for CD34⁺ cells. Additional permeabilization techniques are being tested for these antibodies²³.

WT-1 expression and c-Abl/Bcr-Abl expression were used as a means of sorting CML from normal cells. CML and normal CD34⁺ cells stained with either WT-1 antibody or Abl 24-21 were mixed at equal ratios and sorted based on WT-1 or Abl signal.

Table 7. Enrichment of Bcr-Abl⁺ cells in WT-1^{high} and Abl^{high} fractions of mixed normal and CML CD34⁺ cells.

	Post Sort Ph +
WT-1^{low}	38%
WT-1^{high}	78%
Abl^{low}	25%
Abl^{high}	75%

Sorted cells were analyzed by FISH for Bcr-Abl. Incomplete enrichment was observed for both markers tested (Table 7). Additionally, Abl staining and FACS sorting of CD34⁺ marrow cells from CML patients who had achieved a partial cytogenetic remission on imatinib did not yield any enrichment of Bcr-Abl⁺ cells (data not shown) suggesting that the small differences in signal observed with WT-1 and Abl staining may not be sufficient to achieve the separation necessary for our studies.

In addition to improving staining techniques for candidate markers, additional markers identified by the microarray meta-analysis will be explored with an emphasis on those amenable to cell surface staining.

KEY RESEARCH ACCOMPLISHMENTS

- Analysis of proliferation, cell cycle status, tyrosine phosphorylation and imatinib sensitivity of newly diagnosed CML stem/progenitor cells in an *in vitro* culture system.
- Assessment of the frequency of CML cells among stem cell and quiescent progenitor cell populations of patients in CCR.
- Development of a Bcr-Abl junction-specific antibody capable of distinguishing Bcr-Abl positive and CML cells from normal cells.
- Development of a Bcr-Abl junction-specific molecular beacon capable of distinguishing Bcr-Abl positive cells from Bcr-Abl negative cells.
- Evaluation of seventeen potential markers for CML stem cells.

REPORTABLE OUTCOMES

None to report at this time.

CONCLUSIONS

To address the mechanisms of disease persistence in imatinib-treated CML, we initially studied the *in vitro* effects of imatinib on newly diagnosed CML stem/progenitor cells. We observed inhibition of proliferation of these cells relative to untreated specimens as well as a slight increase in quiescent cells upon imatinib treatment, consistent with previously published data¹². The presence of cycling cells and the net increase in cell number in the presence of imatinib, however, demonstrates that proliferating cells as well as quiescent cells are capable of surviving imatinib treatment. Additionally, we observed inhibition of Bcr-Abl kinase activity in cells surviving imatinib treatment, suggesting that their proliferation and survival were independent of Bcr-Abl activity. A decrease in stem cell markers during the culture period, however, suggests that differentiation had occurred during the culture period. While we can conclude that in the final cell population Bcr-Abl was inhibited by imatinib, it is impossible to extrapolate this result to the starting cell sample.

Because of this difficulty in interpretation of *in vitro* culture studies, we focused on isolating persistent cells from patients in cytogenetic remission. Enrichment strategies using stem cell markers or the property of quiescence did not enrich the Bcr-Abl⁺ population, therefore we focused extensively on methods of Bcr-Abl-specific detection. We generated a Bcr-Abl b3a2 junction-specific antibody capable of selectively recognizing Bcr-Abl expressing cell lines and primary CML progenitors by FACS analysis. We additionally developed a Bcr-Abl b3a2 junction-specific molecular beacon capable of selectively detecting Bcr-Abl mRNA in Bcr-Abl expressing cells. Finally, we evaluated CML progenitor cell markers identified by microarray meta-analysis. Additional experiments will focus on larger scale evaluation and optimization of Bcr-Abl detection in primary CML cells and attempts to isolate persistent CML cells from patients in cytogenetic remission.

The majority of studies to date characterizing mechanisms of disease persistence focus on newly diagnosed or untreated CML cells either newly isolated or cultured *in vitro* to identify imatinib-resistant populations. As our studies have shown, results obtained by this method are complicated by culture-induced changes to the cells. Also, it is impossible to assess whether resistant populations identified by *in vitro* culture behave similarly to persistent CML cells in CCR patients. Through the development of sophisticated methods of CML cell isolation, we hope to study mechanisms of imatinib persistence in pertinent cell populations. This approach will be critical for a thorough understanding of disease persistence and may allow identification of novel drug targets or methods to sensitize resistant cells to imatinib or alternative Bcr-Abl kinase inhibitors.

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20. Jordan CT, Upchurch D, Szilvassy SJ, et al. The interleukin-3 receptor alpha chain is a unique marker for human acute myelogenous leukemia stem cells. *Leukemia*. 2000;14:1777-1784.
21. Gao L, Bellantuono I, Elsasser A, et al. Selective elimination of leukemic CD34(+) progenitor cells by cytotoxic T lymphocytes specific for WT1. *Blood*. 2000;95:2198-2203.
22. Kronenwett R, Butterweck U, Steidl U, et al. Distinct molecular phenotype of malignant CD34(+) hematopoietic stem and progenitor cells in chronic myelogenous leukemia. *Oncogene*. 2005;24:5313-5324.
23. Krutzik PO, Nolan GP. Intracellular phospho-protein staining techniques for flow cytometry: monitoring single cell signaling events. *Cytometry A*. 2003;55:61-70.

APPENDIX

CVs

- Brian Druker, MD – Principal Investigator
- Amie Corbin, BA – Research Associate

BRIAN J. DRUKER

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Born: April 30, 1955 – St. Paul, Minnesota

EDUCATION

B.A., University of California, San Diego, CA	1977
M.D., University of California School of Medicine, San Diego, CA	1981

POSTDOCTORAL TRAINING

<i>Internship and Residency in Internal Medicine</i>	1981-1984
Barnes Hospital, Washington University School of Medicine, St. Louis, MO	
<i>Fellowship in Medical Oncology</i>	1984-1987
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA	

ACADEMIC APPOINTMENTS

<i>Instructor in Medicine</i>	1987-1993
Harvard Medical School, Boston, MA	
<i>Associate Professor</i>	1993-2000
Department of Medicine, Oregon Health & Science University (OHSU)	
<i>Joint Appointment</i>	1993-present
Department of Cell and Developmental Biology, OHSU	
<i>Program Leader</i>	1993-present
Hematologic Malignancies, OHSU Cancer Institute	
<i>Joint Appointment</i>	1996-present
Department of Biochemistry and Molecular Biology, OHSU	
<i>Director / Associate Director</i>	1996-2002
OHSU MD/PhD Program	
<i>Professor of Medicine</i>	2000-present
Division of Hematology & Medical Oncology, OHSU	
<i>Investigator</i>	2002-present
Howard Hughes Medical Institute	

HOSPITAL APPOINTMENTS

<i>Clinical Associate</i>	1987-1993
Dana-Farber Cancer Institute, Boston, MA	
<i>Associate Physician</i>	1987-1993
Brigham and Women's Hospital, Boston, MA	
<i>Medical Director</i>	1987-1993
Nashoba Community Hospital, Oncology Clinic, Ayer, MA	
<i>Staff Physician</i>	1993
University Hospital and Clinics, OHSU	
<i>Co-Director</i>	1993-present
Center for Hematologic Malignancies, OHSU Cancer Institute	

AWARDS AND HONORS

<i>President's Undergraduate Research Award - University of California, San Diego</i>	1976
<i>Phi Beta Kappa</i>	1977
<i>B.A. Summa Cum Laude, University of California, San Diego</i>	1977
<i>American Society for Clinical Investigation</i>	1997
<i>Teaching Award, OHSU 2nd Year Medical School Class</i>	1998
<i>Discovery Award, Oregon Health Sciences Foundation</i>	1999
<i>Lifetime Achievement Award, The Leukemia and Lymphoma Society, Washington Chapter</i>	2000
<i>Translational Research Award, Burroughs Wellcome Fund</i>	2000
<i>Outstanding Alumnus, University of California, San Diego</i>	2000
<i>Distinguished Faculty Award for Outstanding Research, OHSU Foundation & Faculty Senate</i>	2000
<i>John J. Kenny Award, The Leukemia and Lymphoma Society</i>	2000
<i>Charles Rodolphe Brupbacher Prize for Cancer Research</i>	2001
<i>AACR-Richard and Hinda Rosenthal Foundation Award</i>	2001
<i>Emil J. Freireich Award, The University of Texas MD Anderson Cancer Center</i>	2001
<i>Warren Alpert Foundation Prize, Harvard Medical School</i>	2001
<i>Dameshek Prize, The American Society of Hematology</i>	2001
<i>JELD-WEN Chair of Leukemia Research, JELD-WEN, Klamath Falls, Oregon</i>	2001
<i>Donald Ware Waddell Award Lecture, Arizona Cancer Center</i>	2002
<i>Alexandra J. Kefalides Prize for Leukemia Research, University of Pennsylvania Cancer Center</i>	2002
<i>Pioneer of Survivorship Carpe Diem Award, Lance Armstrong Foundation</i>	2002
<i>Medal of Honor, American Cancer Society</i>	2002
<i>Charles F. Kettering Prize, General Motors Cancer Research Foundation</i>	2002
<i>City of Medicine Award, Durham Health Partners, Inc.</i>	2002
<i>Novartis-Drew University Award in Biomedical Research</i>	2002
<i>International Citizen Award, Oregon Consular Corps</i>	2002
<i>Days of Molecular Medicine Translational Medicine Award, UC San Diego-Nature Medicine</i>	2003
<i>David A. Karnofsky Award, American Society of Clinical Oncology</i>	2003
<i>Braunschweig Preis, City of Braunschweig</i>	2003
<i>Member, Institute of Medicine: National Academy of Sciences</i>	2003
<i>Humanitarian Award, The Life Raft Group</i>	2004
<i>Outstanding Program Award, Center for Diversity and Multicultural Affairs, OHSU</i>	2004
<i>Commercialization Award, OHSU</i>	2004
<i>Dr. Alvin J. Thompson Award, Northwest Association for Biomedical Research</i>	2004
<i>Doctor of Science, Honorary Degree, State University of New York</i>	2004
<i>Naomi M. Kanof Clinical Investigator Award, The Society for Investigative Dermatology</i>	2004
<i>Alpha Omega Alpha</i>	2004
<i>David Nathans Memorial Award, Van Andel Institute</i>	2005
<i>Biotech Hall of Fame Award for Scientific Achievement, The Biotech Meeting</i>	2005
<i>Robert-Koch Prize, Robert Koch Foundation</i>	2005
<i>Technology Innovation Award, OHSU</i>	2005
<i>STAR Medical Research Award, Angel Foundation</i>	2006
<i>Member, American Association of Physicians</i>	2006
<i>Technology Innovation Award, OHSU</i>	2006
<i>Golden Plate Award, Academy of Achievement</i>	pending 2007

LICENSURE AND CERTIFICATION

<i>Diplomate, National Board of Medical Examiners</i>	1982
<i>Massachusetts License Registration No. 52706</i>	1984-1993
<i>American Board of Internal Medicine</i>	1985
<i>American Board of Internal Medicine, Medical Oncology</i>	1987
<i>Oregon Board of Medical Examiners No. 18379</i>	1993

PROFESSIONAL AFFILIATIONS

American Association for the Advancement of Science (AAAS)
 American Society of Hematology (ASH)
 American Society for Microbiology (ASM)
 American Society for Clinical Investigation (ASCI)
 American Society of Clinical Oncology (ASCO)
 American Association for Cancer Research (AACR)
 Children's Oncology Group (COG)
 The American Society for Cell Biology (ASCB)

MAJOR RESEARCH INTERESTS

- Identification and characterization of substrates of activated tyrosine kinases with specific emphasis on the BCR-ABL tyrosine kinase
- Evaluation of specific ABL tyrosine kinase inhibitors as mechanism based therapeutic agents for chronic myelogenous leukemia
- Identification of molecular pathogenetic events in leukemia with specific emphasis on tyrosine kinases and development of inhibitors of these kinases
- Clinical trials of molecularly targeted agents

TEACHING RESPONSIBILITIES AT OHSU

<i>Lecturer</i> , CON 654: Topics in Signal Transduction, Graduate	1993-present
<i>Lab Instructor/Lecturer</i> , MSCI 623: Pathophysiology of Blood, 2nd year Medical	1994-present
<i>Lab Instructor</i> , BBOD: Biology of Neoplasia, 1st year Medical	1994-present
<i>Lecturer</i> , CELL 616: Cancer Biology, Graduate	1994-present
<i>Lecturer</i> , CON 653: Molecular & Cell Biology II Eukaryotic Cell Biology, Graduate	1995-present
<i>Lecturer</i> , Fellows Training Course	1997-present
<i>Lecturer</i> , HIP 514: Molecular Biology for Clinical Research, Continuing	2005-present
<i>Lecturer</i> , CON 665: Development, Differentiation and Cancer, Graduate	2005-present

GRANT REVIEW

American Society of Hematology, Fellow and Junior Scholar Awards	1997
Damon Runyon-Lilly Clinical Investigator Award Committee	2003-2005
Department of Defense Chronic Myelogenous Leukemia Research Program, Ad Hoc Reviewer	2004
Doris Duke Charitable Foundation, Clinical Scientist Development Award, Reviewer	2001-2005
Fanconi Anemia Research Fund	1996, 1997
Israel Science Foundation, Ad Hoc Reviewer	2000
National Institutes of Health (NIH)	
Hematology Study Section I, Ad Hoc Reviewer	1995, 1996
Hematology Study Section I, Permanent Member	1997-2001
M.D. Anderson Cancer Center, CML Program Project Grant	1994
National Cancer Institute (NCI)	
▪ Cold Spring Harbor Cancer Center Grant	1995
▪ Thomas Jefferson University, Cancer Center Grant	1994, 1998
National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)	
▪ Centers of Excellence, Molecular Hematology	1994
Oncological Sciences, Special Emphasis Panel, Myeloid Leukemia	2005
XVII International Symposium for Comparative Research on Leukemia and Related Diseases	1994
United States-Israel Binational Science Foundation, Ad Hoc Reviewer	1996
VA Merit Award, Ad Hoc Reviewer	1995, 1996, 1997

MANUSCRIPT REVIEW & EDITORIAL RESPONSIBILITIES

<i>Editorial Board, Blood</i>	1998-2002
<i>Editorial Board, Cancer Cell</i>	2001-present
<i>Editorial Board, Cell Cycle</i>	2002-present
<i>Senior Editor, Molecular Cancer Therapeutics</i>	2003-present
<i>Senior Editor, Hematologic Malignancies, Hem/Onc Today</i>	2005-present
<i>Editorial Advisory Board, Handbook of Genomic Medicine</i>	2005-present
<i>Associate Editor, Blood</i>	2006-present
<i>Ad hoc reviewer:</i> British Journal of Haematology • Cancer Research • Clinical Cancer Research • Experimental Hematology • Journal of Biological Chemistry • Journal of Clinical Investigation • Journal of Clinical Oncology • Journal of the American Medical Association • The New England Journal of Medicine • Proceedings of the National Academy of Science	

COMMITTEE & BOARD MEMBERSHIP

American Association for Cancer Research	
Board of Directors	2002-2005
Clinical and Experimental Therapeutic Awards, Selection Committee	2003-2004
2005 Pezcoller Foundation-AACR International Award for Cancer Research Selection Committee	2004
Clinical Research and Experimental Therapeutics Awards, Nominating Committee	2004-2005
2005 Award for Lifetime Achievement in Cancer Research, Selection Committee	2004-2005
2006 Pezcoller Foundation-AACR International Award for Cancer Research, Nominating Committee	2005
American Society of Clinical Oncology, Program Committee Member: Adult Leukemia & Lymphoma	2001-2002
American Society of Hematology, Scientific Committee on Neoplasia	2000-2004
American Medical Informatics Association: Global Trial Bank, Steering Committee	2005-present
Institute of Medicine, Cancer and Cancer Biology Interest Group	2005-present
The Leukemia & Lymphoma Society	
Oregon Chapter Board of Trustees	1993-2003
National Board of Trustees	2002-2003
▪ Medical and Scientific Affairs Committee	2001-present
- Professional Education Subcommittee	2004-present
▪ Brand Communications Committee	2002-2004
Concert/Collaborations Resource Team	2006-present
Research Foundation	2006-present
Co-Chair, Search Committee for Executive Vice President	2006
The Max Foundation, Scientific Medical Board	2002-present
Multiple Myeloma Research Consortium, External Advisory Board	2004-present
National Cancer Institute	
Molecular Targets Working Group, Organ Systems Branch	2003-2004
Advanced Biomedical Technology Development Working Group, National Cancer Advisory Board (Chair, Cancer Therapeutics Focus Group)	2003-2005
External Scientific Committee, NHGRI Human Cancer Genome Project	2005-present
▪ Ethics, Law, & Policy Subcommittee	2005-present
National Institutes of Health, Advisory Committee to the Director: Working Group on the Protection of the Taxpayers' Interests	2003-2004

Oregon Health & Science University	
Senior Leadership Council, OHSU Cancer Institute	1993-present
▪ Executive Committee	1993-present
Search Committee, Endowed Chair – Cancer Research	1994-1995
Institutional Review Board	1994-1997
Heme/Onc Fellowship Task Force	1995
Department of Medicine Task Force for Faculty Productivity	1995
Internal Advisory Board, Center for the Study of Weight Regulation	2003-present
Internal Advisory Board, Stem Cell Biology Center	2004-present
Research Council	2004-2006
Research Steering Plan Committee	2006-present
Research Strategic Plan Committee	1998-1999
Founding Member, Oregon Clinical and Translational Science Institute (OCTSI)	2006-present
Public Library of Science (PLOS), Board of Directors	2003-present
Southwest Oncology Group, Leukemia Committee	2006-present
▪ Leukemia Translational Medicine Subcommittee	2006-present
University of California San Diego, Rebecca and John Moores UCSD Cancer Center	
External Scientific Advisory Board	2004-present
University of Minnesota Cancer Center and School of Pharmacy,	
Experimental Therapeutics Scientific Advisory Committee	2004-present

BIBLIOGRAPHY

Original Publications

1. Wepsic HT, Alaimo J, Druker BJ, Murray W IV, Morris HP. The negative systemic effect of BCGw inoculated intraperitoneally. I. In vivo demonstration of intramuscular tumor growth enhancement using Morris hepatomas. *Cancer Immunol Immunother* 10:217-225, 1981.
2. Druker BJ, Wepsic HT, Alaimo J, Murray W IV. The negative systemic effect of BCGw inoculated intraperitoneally. II. The in vitro demonstration of the presence of suppressor cells in BCGw immunized rats. *Cancer Immunol Immunother* 10:227-237, 1981.
3. Druker BJ, Wepsic HT, Alaimo JC, Murray W IV, Vranes AJ. Identification and characterization of the BCG cell wall-stimulated suppressor cells in inbred rats. *Intl J Oncodevel Biol Med* 3:209-221, 1982.
4. Druker BJ and Wepsic HT. Identification and characterization of the BCG. *Cancer Invest* 1:151-161, 1983.
5. Draetta G, Piwnica-Worms H, Morrison D, Druker B, Roberts T, Beach D. Human cdc2 protein kinase is a major cell-cycle regulated tyrosine kinase substrate. *Nature* 336:738-744, 1988.
6. Druker BJ, Rosenthal DR, Canellos GP. Chlorambucil, vinblastine, procarbazine and prednisone: an effective but less toxic regimen than MOPP for advanced-stage Hodgkin's disease. *Cancer* 63:1060-1064, 1989.
7. Druker BJ, Mamon HJ, Roberts TM. Oncogenes, growth factors and signal transduction. *N Engl J Med* 321:1383-1391, 1989.
8. Varticovski L, Druker B, Morrison D, Cantley L, Roberts T. The colony stimulating factor-1 receptor associates with and activates phosphatidylinositol-3 kinase. *Nature* 342:699-702, 1989.
9. Druker BJ, Ling LE, Cohen B, Roberts TM, Schaffhausen BS. A completely transformation-defective point mutant of polyomavirus middle T antigen which retains full associated phosphatidylinositol kinase activity. *J Virol* 64:4454-61, 1990.
10. Cohen B, Liu Y, Druker B, Roberts TM, Schaffhausen BS. Characterization of pp85, a target of oncogenes and growth factor receptors. *Mol Cell Biol* 10:2909-2915, 1990.

11. Epstein RJ, Druker BJ, Roberts TM, Stiles CD. Modulation of a 175,000 M_r c-neu receptor isoform in G8/DHFR cells by serum starvation. *J Biol Chem* 265:10746-10751, 1990.
12. Kanakura Y, Druker B, Cannistra SA, Furukawa Y, Torimoto Y, Griffin JD. Signal transduction of the human granulocyte-macrophage colony-stimulating factor and interleukin-3 receptors involves tyrosine phosphorylation of a common set of cytoplasmic proteins. *Blood* 76:706-715, 1990.
13. Kanakura Y, Druker B, Wood KW, Mamon HJ, Okuda K, Roberts TM, Griffin JD. Granulocyte-macrophage colony-stimulating factor and interleukin-3 induce rapid phosphorylation and activation of the proto-oncogene raf-1 in a human factor-dependent myeloid cell line. *Blood* 77:243-248, 1991.
14. Kanakura Y, Druker B, DiCarlo J, Cannistra SA, Griffin JD. Phorbol 12-myristate 13-acetate inhibits granulocyte-macrophage colony stimulating factor-induced protein tyrosine phosphorylation in a human factor-dependent hematopoietic cell line. *J Biol Chem* 266:490-495, 1991.
15. Vivier E, Morin P, O'Brien C, Druker B, Schlossman SF, Anderson P. Tyrosine phosphorylation of the FcγRIII (CD16): ζ complex expressed by human natural killer cells. *J Immunol* 146:206-210, 1991.
16. Burgess KE, Odysseos AD, Zalvan C, Druker BJ, Anderson P, Schlossman SF, Rudd CE. Biochemical identification of a direct physical interaction between the CD4:p56^{lck} and T_i(TcR)/CD3 complexes. *Eur J Immunol* 21:1663-1668, 1991.
17. Longnecker R, Druker B, Roberts TM, Kieff E. An Epstein-Barr virus protein associated with cell growth transformation interacts with a tyrosine kinase. *J Virol* 65:3681-3692, 1991.
18. Davis S, Lu ML, Lo SH, Lin S, Butler JA, Druker BJ, Roberts TM, An Q, Chen LB. Presence of an Sh2 domain in the actin-binding protein tensin. *Science* 252:712-715, 1991.
19. Ley SC, Davies AA, Druker B, Crumpton MJ. The T cell receptor/CD3 complex and CD2 stimulate the tyrosine phosphorylation of indistinguishable patterns of polypeptides in the human T leukemia cell line Jurkat. *Eur J Immunol* 21:2203-2209, 1991.
20. Okuda K, Druker B, Kanakura Y, Koenigsman M, Griffin JD. Internalization of the granulocyte-macrophage colony-stimulating factor receptor is not required for induction of protein tyrosine-phosphorylation in human myeloid cells. *Blood* 78:1928-1935, 1991.
21. Kuriu A, Ikeda A, Kanakura Y, Griffin JD, Druker B, Yagura H, Kitayama H, Ishikawa J, Nishiura T, Kanayama Y, Yonezawa T, Tarui S. Proliferation of human myeloid leukemia cell line associated with the tyrosine phosphorylation and activation of the proto-oncogene c-kit product. *Blood* 78:2834-2840, 1991.
22. Druker BJ and Roberts TM. Generation of a large library of point mutations in polyoma middle T antigen. *Nucl Acids Res* 19:6855-6861, 1991.
23. Held JL, Druker BJ, Kohn SR, Byrnes W, Margolis RJ. Atypical, nonfatal, transfusion-associated, acute graft-versus-host disease in a patient with Hodgkin's disease. *J Am Acad Dermatol* 26:261-262, 1992.
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26. Ling LE, Druker BJ, Cantley LC, Roberts TM. Transformation-defective mutants of polyoma-virus middle T antigen associate with phosphatidylinositol 3-kinase (PI 3-kinase) but are unable to maintain wild-type levels of PI 3-kinase products in intact cells. *J Virol* 66:1702-1708, 1992.

27. Oda A, Druker BJ, Smith M, Salzman EW. Inhibition by sodium nitroprusside or PGE₁ of tyrosine phosphorylation induced in platelets by thrombin or ADP. *Am J Physiology* 262:701-707, 1992.
28. Bachelot C, Cano E, Grelac F, Saleun S, Druker BJ, Levy-Toledano S, Fischer S, Rendu F. Functional implications of tyrosine protein phosphorylation in platelets: simultaneous studies with different agonists and inhibitors. *Biochem J* 284:923-928, 1992.
29. Epstein R, Druker BJ, Irminger J-C, Jones SD, Roberts TM, Stiles CD. Extracellular calcium mimics the actions of platelet-derived growth factor on mouse fibroblasts. *Cell Growth and Differentiation* 3:157-164, 1992.
30. Okuda K, Sanghera JS, Pelech SL, Kanakura Y, Hallek M, Griffin JD, Druker BJ. Granulocyte-macrophage colony-stimulating factor, interleukin-3, and steel factor induce rapid tyrosine phosphorylation of p42 and p44 MAP kinase. *Blood* 79:2880-2887, 1992.
31. Druker BJ, Sibert L, Roberts TM. Polyomavirus middle T-antigen NPTY mutants. *J Virol* 66:5770-5776, 1992.
32. Druker B, Okuda K, Matulonis U, Salgia R, Roberts T, Griffin JD. Tyrosine phosphorylation of rasGAP and associated proteins in chronic myelogenous leukemia cell lines. *Blood* 79:2215-2220, 1992.
33. Epstein RJ, Druker BJ, Roberts TM, Stiles CD. Synthetic phosphopeptide immunogens yield activation-specific antibodies to the c-erbB-2 receptor. *Proc Natl Acad Sci USA* 89:10435-10439, 1992.
34. Hallek M, Druker B, Lepisto EM, Wood KW, Ernst TJ, Griffin JD. Granulocyte-macrophage colony-stimulating factor and steel factor induce phosphorylation of both unique and overlapping signal transduction intermediates in a human factor-dependent hematopoietic cell line. *J Cell Physiol* 153:176-186, 1992.
35. Oda A, Druker BJ, Smith M, Salzman EW. Association of pp60src with Triton X-100-insoluble residue in human blood platelets requires platelet aggregation and actin polymerization. *J Biol Chem* 267:20075-20081, 1992.
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39. Matulonis U, Salgia R, Okuda K, Druker B, Griffin JD. Interleukin-3 and p210 BCR/ABL activates both unique and overlapping pathways of signal transduction in a factor-dependent myeloid cell line. *Exp Hematol* 21:1460-1466, 1993.
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50. Dusanter-Fourt I, Muller O, Ziemiecki A, Mayeux P, Druker B, Djiane J, Wilks A, Harpur AG, Fischer S, Gisselbrecht S. Identification of JAK protein tyrosine kinases as signaling molecules for prolactin. Functional analysis of prolactin receptor and prolactin-erythropoietin receptor chimera expressed in lymphoid cells. *EMBO J* 13:2583-2591, 1994.
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