HLA class I and II genotype of the NCI-60 cell lines
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Abstract
Sixty cancer cell lines have been extensively characterized and used by the National Cancer Institute's Developmental Therapeutics Program (NCI-60) since the early 90's as screening tools for anti-cancer drug development. An extensive database has been accumulated that could be used to select individual cells lines for specific experimental designs based on their global genetic and biological profile. However, information on the human leukocyte antigen (HLA) genotype of these cell lines is scant and mostly antiquated since it was derived from serological typing. We, therefore, re-typed the NCI-60 panel of cell lines by high-resolution sequence-based typing. This information may be used to: 1) identify and verify the identity of the same cell lines at various institutions; 2) check for possible contaminant cell lines in culture; 3) adopt individual cell lines for experiments in which knowledge of HLA molecule expression is relevant. Since genome-based typing does not guarantee actual surface protein expression, further characterization of relevant cell lines should be entertained to verify surface expression in experiments requiring correct antigen presentation.

Background
A panel of sixty cancer cell lines of diverse lineage (lung, renal, colorectal, ovarian, breast, prostate, central nervous system, melanoma and hematological malignancies) was developed, characterized and extensively used by the National Cancer Institute's Developmental Therapeutics Program (NCI-60) since the early 90's as a screening tool for anti-cancer drug development [1]. This strategy [2-9] yielded data about drug-related cytotoxicity for about 100,000 compounds. In addition, extensive functional characterization of the NCI-60 response to diverse biological or chemical stimulation has been accumulated [10-15]. Although originally developed for chemo-sensitivity testing, with the development of high-throughput analyses the NCI-60 panel has been broadly characterized for other biological applications [16-25]. Thus, patterns incidentally identified provided platforms for further investigations of mechanisms of tumorigenesis and cancer progression [5,6,26-30]. More recently, genomic DNA [24] and proteomics analyses have further characterized the profile of these cell lines [31]. The combined database provides the most comprehensive phenotyping of commonly accessible cancer cell lines offering correlative information about genetic, transcriptional and post-trans-
Table 1: Available information from the ATCC about the NCI-60 panel

| Name       | ATCC no. | Sex | Race | Tumor Type | ATCC HLA typing | Discrepant |
|------------|----------|-----|------|------------|-----------------|------------|
| BT-549     | HTB-122  | F   | C    | Breast CA  |                 |            |
| HS 578T    | HTB-126  | F   | C    | Breast CA  |                 |            |
| MCF7       | HTB-22   | F   | C    | Breast CA  |                 |            |
| MDA-MB-231 | HTB-26   | F   | C    | Breast CA  |                 |            |
| MDA-MB-435 | HTB-129  | F   | C    | Breast CA  |                 |            |
| T-47D      | HTB-133  | F   |      | Breast CA  |                 |            |
| SF-268     |          |     |      | CNS CA     |                 |            |
| SF-295     |          |     |      | CNS CA     |                 |            |
| SF-539     |          |     |      | CNS CA     |                 |            |
| SNB-19     |          |     |      | CNS CA     |                 |            |
| SNB-75     |          |     |      | CNS CA     |                 |            |
| U251       |          |     |      | CNS CA     |                 |            |
| COLO 205   | CCL-222  | M   | C    | Colon CA   |                 |            |
| HCC-2998   |          |     |      | Colon CA   |                 |            |
| HCT-116    | CCL-247  | M   | C    | Colon CA   |                 |            |
| HCT-15     | CCL-225  | M   | C    | Colon CA   |                 |            |
| HT29       | HTB-38   | F   | C    | Colon CA   |                 |            |
| KM12       |          |     |      | Colon CA   |                 |            |
| SW-620     | CCL-227  | M   | C    | Colon CA   |                 |            |
| MOL-4      | CRL-1582 | M   |      | Leukemia, ALL |             |            |
| CCRF-CEM   | CCL-119  | F   | C    | Leukemia, ALL |         |            |
| HL-60      | CCL-240  | F   | C    | Leukemia, APL |            |            |
| K-562      | CCL-243  | F   |      | Leukemia, CML |            |            |
| SR         | CRL-2262 | M   | C    | Leukemia, LCIL |          |            |
| LOX IMVI   |          |     |      | Melanoma   |                 |            |
| M 14       |          |     |      | Melanoma   |                 |            |
| SK-MEL-2   | HTB-68   | M   | C    | Melanoma   |                 |            |
| SK-MEL-5   | HTB-70   | F   | C    | Melanoma   |                 |            |
| SK-MEL-28  | HTB-72   | M   | C    | Melanoma   | A2,11, B40,Bw16 | Yes        |
| UACC-62    |          |     |      | Melanoma   |                 |            |
| UACC-257   |          |     |      | Melanoma   |                 |            |
| RPMI 8226  | CCL-155  | M   |      | MM         | A1,3,B12,17 Cw5 | Yes        |
| A549/ATCC  | CCL-185  | M   | C    | NSCLC      | A1,26, B40,DRw4 | Yes        |
| EKVX       |          |     |      | NSCLC      |                 |            |
| HOP-62     |          |     |      | NSCLC      |                 |            |
| HOP-92     |          |     |      | NSCLC      |                 |            |
| NCI-H23    | CRL-5800 | M   | AA   | NSCLC      |                 |            |
| NCI-H226   | CRL-5826 | M   |      | NSCLC      |                 |            |
| NCI-H322M  |          |     |      | NSCLC      |                 |            |
| NCI-H460   | HTB-177  | M   |      | NSCLC      |                 |            |
| NCI-H522   | CRL-5810 | M   | C    | NSCLC      |                 |            |
| IGROV1     | HTB-161  |     |      | Ovarian CA |                 |            |
| OVCAR-3    |          |     |      | Ovarian CA |                 |            |
| OVCAR-4    |          |     |      | Ovarian CA |                 |            |
| OVCAR-5    |          |     |      | Ovarian CA |                 |            |
| OVCAR-8    |          |     |      | Ovarian CA |                 |            |
| NCI/ADR-RES|          |     |      | Ovarian CA |                 |            |
| SK-OV-3    | HTB-77   | F   | C    | Ovarian CA |                 |            |
| DU-145     | HTB-81   | M   | C    | Prostate CA | A1,9         | No          |
| PC-3       | CRL-1435 | M   | C    | Prostate CA | A1,9         | No          |
| 786-O      |          |     |      | Renal CA   |                 |            |
| A498       | HTB-44   | F   |      | Renal CA   |                 |            |
Table 1: Available information from the ATCC about the NCI-60 panel (Continued)

| Cell Line | ATCC No. | Source | HLA Genotype | Notes |
|-----------|----------|--------|--------------|-------|
| A9, B12, 25 |          |        |              |       |
| AA = African American; ALL = Acute Lymphoblastic Leukemia; APL = Acute promyelocytic leukemia; C = Caucasian; CA = Carcinoma; CML = Chronic Myelogenous Leukemia; CNS = Central Nervous System; F = Female; LCIL = Large Cell Immunoblastic Lymphoma; M = Male; MM = Multiple Myeloma; NA = Not Available; NSCLC = Non Small Cell Lung Cancer.

The information about the ATCC cell lines (Cell Lines with ATCC no.) was obtained accessing the following URL: http://www.atcc.org. Additional information was obtained through the National Cancer Institute’s Developmental Therapeutics Program URL: http://dtp.nci.nih.gov/branches/btb/tumor-catalog.pdf.

Results and Discussion

Previous knowledge of the HLA phenotype of NCI-60 cell lines

We reviewed and collected available information about the HLA phenotype of the NCI-60 cell lines, performed according to serological testing before submission to the ATCC (Table 1). The information was collected through the ATCC website: http://www.atcc.org. Most cell lines had not been previously typed; the large majority of the cell lines from which such information is available had been developed from Caucasian patients. HLA typing was reported according to the old serologic nomenclature at a very low level of resolution. In addition, several reported typings did not match the present typing as shown in Table 2 and 3. This was the case for the colon carcinoma cell line HT29 that maintained a correct haplotype (with the exclusion of the HLA-Cw locus) but had a completely different second haplotype. The melanoma cell line SK-MEL-5 had an almost identical haplotype with the exception of one HLA-B allele originally typed as Bw16 (inclusive of the molecularly-defined alleles: B*38 and B*39), while the present typing was HLA-B*07. Another melanoma cell line SK-MEL-28 maintained a haplotype similar to the previously reported HLA-A11, -B40 but appeared to have lost an HLA-A allele (HLA-A26) compared with the original ATCC description. Finally, the multiple myeloma cell line RPMI 8226 was matched at one haplotype (HLA-A19, -B15 and -Cw2) but was totally discrepant at the second haplotype (HLA-A*6802, -B*1510 and -Cw*0304). The HLA typing of the other two previously typed cell lines was confirmed in the present study. Overall, in spite of the discrepancies in HLA typing observed between the previous and the present analyses, a resemblance was noted in the cell line genotype suggesting that mis-typing related to the low accuracy of serological methods might have been at the basis of the discrepancy rather than contamination or switching of the cell lines.

Overall, there was no evidence of contamination among the cell lines tested with clean homozygous or heterozygous combinations observed in all loci analyzed. SBT of HLA class I and HLA class II loci are reported in Table 2 and 3 respectively. Information about the HLA typing of the cell lines is also available through the Molecular Targets URL: http://dtp.nci.nih.gov/mtargets/mt_index.html. Approximately 17% of the cell lines (10 out of 58 including: T47D, SNB-19, U251, KM12, RPMI-8226, EKVX, NCI-H23, NCI-H322M, A498, ACHN and TK-10) exhibited a pseudo-homozygous pattern suggestive of complete loss of heterozygosity encompassing the HLA class I and HLA class II regions. This frequency is close to the loss of...
Table 2: Sequence-based typing of NCI-60 HLA class I Loci

| Cell Line ID | Tissue | A locus | B Locus | Cw Locus |
|-------------|--------|---------|---------|----------|
| BT-549      |        | N.R.    | 151701, 5501 | 030301, 07a |
| HS 578T     |        | 03, 24a | 35, 40a | 030401, 04a |
| MCF7        |        | 020101  | 18, 44a | 05a |
| MDA-MB-231  |        | 0201, 0217 | 4002, 4101 | 020202, 17a |
| MDA-MB-435  |        | 110101, 240201 | 15, 35a | 030301, 04a |
| T47D        |        | 3301    | 1402    | 0802 |
| SF-268      |        | 010101, 3201 | 0801, 4002 | 020202, 07a |
| SF-295      |        | 010101, 2601 | 070201, 5501 | 07a, 07a |
| SF-539      |        | 020101  | 08, 35a | 04a, 07a |
| SNB-19      |        | 020101  | 18      | 05a |
| SNB-75      |        | 020101, 110101 | 35, 39a | 04a, 120301 |
| U251        |        | 020101  | 18      | 05a |
| COLO 205    |        | 01, 02a | 07, 08a | 070201, 07a |
| HCC-2998    |        | 02, 24a | 3701, 400601 | 04a, 0602 |
| HCT-116     |        | 01, 02a | 18, 4501 | 05a, 07a |
| HCT-15      |        | 02, 24a | 08new, 350101 | 04a, 07a |
| HT29        |        | 01, 24a | 35, 440301 | 04a |
| KM12        |        | 02new   | 70201   | 70201 |
| SW-620      |        | 02, 24a | 07, 15a | 070201, 07a |
| MOLT 4      |        | 010101, 2501 | 18, 570101 | 0602, 120301 |
| CCRF-CEM    |        | N.R.    | 08, 40a | 030401, 07a |
| HL-60       |        | 10101   | 570101  | 0602 |
| K-562       |        | 110101, 310102 | 18, 40a | 03a, N.R. |
| SK          |        | 02, 03a | 3701, 3901 | 0602, 120301 |
| LOX IMVI    |        | 110101, 2902 | 070201, 440301 | 070201, 1601 |
| M 14        |        | 110101, 240201 | 15, 35a | 030301, 04a |
| SK-MEL-2    |        | 03, 26a | 35, 38a | 04a, 120301 |
| SK-MEL-5    |        | 020101, 110101 | 07, 40a | 030401, 070201 |
| SK-MEL-28   |        | 110101 | 4001    | 030401 |
| UACC-62     |        | 02, 32a | 39, 44a | 05a, 12a |
| UACC-257    |        | 020101 | 18, 44a | 05a, 07a |
| RPMI-8226   |        | 3001, 6802 | 1503, 1510 | 020204, 030402 |
| A549/ATCC   |        | 2501, 3001 | 18, 440301 | 120301, 1601 |
| EKXV        |        | 010101  | 3701    | 0602 |
| HOP-62      |        | 030101  | 07, 44a | 05a, 070201 |
| HOP-92      |        | 030101  | 07, 44a | 070201 |
| NCI-H23     |        | 8001    | 5001    | 0602 |
| NCI-H226    |        | 010101, 240201 | 07, 39a | 070201, 120301 |
| NCI-H322M   |        | 010101  | 2902    | 440301 |
| NCI-H460    |        | 031301  | 24, 68a | 35, 51a | 03a, 15a |
| NCI-H522    |        | 020101  | 44, 5501 | 030301, 05a |
| IGROV1      |        | 240201, 3301 | 4901 | 07a |
| OVCAR-3     |        | 020101, 2902 | 070201, 5801 | 070201, 07a |
| OVCAR-4     |        | 010101, 3201 | 0801, 4002 | 07a, 15a |
| OVCAR-5     |        | 01, 02a | 08, 44a | 05a, 07a |
| OVCAR-8     |        | 010101, 2501 | 570101 | 0602 |
| NCI-ADR-RES |        | 010101, 2501 | 570101 | 0602 |
| SK-OV-3     |        | 03, 68a | 18, 35a | 04a, 05a |
| DU-145      |        | 030101, 3303 | 5001, 570101 | 0602 |
| PC-3        |        | 010101, 240201 | 1302, 5501 | 01a, 06a |
| 786-O       |        | 030101  | 07, 44a | 05a, 070201 |
| A498        |        | 020101  | 0801    | 07a |
haplotype that we originally described for melanoma cell lines generated at the National Cancer Institute (Bethesda, MD) [38,39] and subsequently observed in other cancers [40,41]. We conclude that this is an unlikely representative of patients' homozygosity because complete HLA class I and II homozygosity is exceedingly rare in the population at large. To corroborate this statement, we analyzed 554 genomic DNA specimens from normal donors recently typed with the same technology in our laboratory. Genomic DNA for the normal donors was obtained from whole blood samples. Only 5 individuals were found to be truly homozygous for all HLA class I and class II loci for a frequency of 0.9%.

Overall, discrepancies between ATCC typings and the present typing or the unbalanced frequency of homozygosity could be related to accumulated genetic alterations between the cell lines since the time of their original expansion from the patient and should not be surprising.

A particular case was represented by the NCI/ADR-RES cell line which was previously believed to be an adriamycin derivative of the breast cancer cell line MCF-7. Subsequently, it was discovered not to be related to MCF-7, but it's derivation was unclear [42]. Karyotyping analysis suggested it was related to the ovarian cell line OVCAR-8. Subsequent DNA fingerprinting confirmed that both cell lines were generated from the same individual. HLA genotyping confirms this since the cell lines are indeed identical.

To avoid possible misinterpretations, a large number of alleles are not presented here with their definitive nomenclature but rather at a two digits level of resolution because some of the ambiguities could not be completely resolved by SBT as previously described [43]. However, more detailed information about individual cell lines can be obtained by contacting Sharon Adams directly at the HLA laboratory, Department of Transfusion Medicine, Bethesda, MD. As previously described [43], it is possible to resolve most of these ambiguities using various methods including sequence-specific primer PCR or pyrosequencing [44]. If necessary in the future, the NIH HLA laboratory may assist in further characterization of individual HLA alleles. Another caveat is that the identification of HLA alleles at the genomic level does not necessarily correspond to surface expression of their protein products since various abnormalities in transcription, translation and assembling could influence the surface expression of HLA molecules [39,45,46].

Finally, several new alleles were identified (referred to in the tables as new, for which a nomenclature is pending; in detail KM12 HLA-A*02new = Genbank Accession # AY918166; SN12C HLA-A*24new = # AY918167; CAKI-1 HLA-Cw04new = # AY918170). Information regarding the sequence of these alleles could be obtained by directly contacting the HLA laboratory, Department of Transfusion Medicine, Bethesda, MD.

### Materials and Methods

#### Cell Lines

Genomic DNA from the NCI-60 cell line anticancer drug discovery panel was obtained from SH of the National Cancer Institute Developmental Therapeutics Program (Bethesda, MD). Cells were grown in RPMI 1640 supplemented with 10% fetal bovine serum and 5 mM L-glutamine.

#### DNA Isolation

Genomic DNA was isolated from peripheral blood using the Gentra PUREGENE isolation kit (Gentra Systems, Minneapolis, MN, USA). The DNA was re-suspended in Tris HCl buffer (pH 8.5) and the concentration was measured using a Pharmacia Gene Quant II Spectrophotometer. The DNA was then stored at -70°C until testing.

#### Sequence-Based Typing (SBT)

HLA class I loci sequence-based typing (SBT) was performed as previously described [43]. The primary PCR amplification reaction produced a 1.5 kb amplicon encompassing exon 1 through intron 3 of the HLA class I locus. All reagents necessary for primary amplification and sequencing were included in the HLA-A, HLA-B and
Table 3: Sequence-based typing of NCI-60 HLA class II Loci

| Cell Line | ID     | Tissue     | DRβ1 Locus | DQB1 Locus | DPβ1 Locus |
|-----------|--------|------------|------------|------------|------------|
| BT-549    | 41292-D| Breast CA  | 11a, 13a   | 030101, 060401 | 020102, 0401 |
| HS 578T   | 41293-D| Breast CA  | 01a, 150101| 050101, 0602 | 0401, 7801  |
| MCF7      | 41294-D| Breast CA  | 03a, 15a   | 0201, 0602  | 020102, 0401 |
| MDA-MB-231| 41296-D| Breast CA  | 0701, 1305 | 0202, 030101| 020102, 1701 |
| MDA-MB#35 | 41297-D| Breast CA  | 040501, 130101| 0302, 0603 | 1301, 1901  |
| T47D      | 41298-D| Breast CA  | 010201     | 050101     | 020102, 0401 |
| SF-268    | 41286-D| CNS CA     | 03a, 04a   | 0201, 0302  | 0401, 0601  |
| SF-295    | 41287-D| CNS CA     | 14a, 15a   | 050301, 0602| 0401        |
| SF-539    | 41288-D| CNS CA     | 030101, 12a| 0201, 030101| 010101, 0401 |
| SNB-19    | 41289-D| CNS CA     | 030101     | 0201       | 0402        |
| SNB-75    | 41290-D| CNS CA     | 0103, 11a  | 03a, 050101| 0401, 0402  |
| U251      | 41291-D| CNS CA     | 030101     | 0201       | 0402        |
| COLO 205  | 41299-D| Colon CA   | 040101, 130101| 0603     | 0401        |
| HCC-2998  | 41300-D| Colon CA   | 11a, 16a   | 030101, 050201| 0401        |
| HCT-116   | 41301-D| Colon CA   | N.R.       | 02new, 03new| 030101, 0402 |
| HCT-15    | 41302-D| Colon CA   | 03a, 14a   | 02a, 050301| 010101, 0401 |
| HT29      | 41303-D| Colon CA   | 0402, 0701 | 02a, 0302  | 0401        |
| KM12      | 41304-D| Colon CA   | 040101     | 0302       | 1301        |
| SW-620    | 41305-D| Colon CA   | 0103, 130101| 050101, 0603| 010101, 0401 |
| MOLT 4    | 41281-D| Leukemia, ALL| 07new, 12new| 0202, 030101| 20102       |
| CCRF-CEM  | 41282-D| Leukemia, ALL| 030101, 0701| 0201, 0202| 0401, 1301  |
| HL-60     | 41284-D| Leukemia, APL| N.R.       | 030302     | 0401, 1301  |
| K-562     | 41280-D| Leukemia, CML| 03a, 04a   | 0201, 0302  | 0401, 0402  |
| K      | 41285-D| Leukemia, LCIL| 01a, 160101| 050101, 050201| 0401        |
| LOX IMVI  | 41315-D| Melanoma   | 0701, 150101| 0202, 0602  | 0401, 110101 |
| M 14      | 41316-D| Melanoma   | 040501, 130101| 0302, 0603 | 1301, 1901  |
| SK-MEL-2  | 41317-D| Melanoma   | 0402, 130101| 030101, 0603| 020102, 0401 |
| SK-MEL-5  | 41319-D| Melanoma   | 040101, 130101| 0302, 0603 | 030101, 1601 |
| SK-MEL-28 | 41318-D| Melanoma   | 0404       | 0302       | 030101      |
| UACC-62   | 41321-D| Melanoma   | 12a, 130101| 030101, 0603| 0401, 1401  |
| UACC-257  | 41320-D| Melanoma   | 040101     | 030101, 0302| 0401        |
| RPMI-8226 | 41283-D| MM         | 030101, 0701| 0201, 0202  | 010102, 1301 |
| AS49/ATCC | 41306-D| NSCLC      | 0701, 110401| 0202, 030101| N.R.        |
| EKXV      | 41307-D| NSCLC      | 150101     | 0602       | 0401        |
| HOP-62    | 41308-D| NSCLC      | 13a, 15a   | 06a, 06a   | 0402        |
| HOP-92    | 41309-D| NSCLC      | 01a, 150101| 050101, 0602| 0401, 0402  |
| NCI-H23   | 41312-D| NSCLC      | 130101     | 0603       | 1901        |
| NCI-H226  | 41311-D| NSCLC      | 150101, 160101| 050201, 0602| 020102, 0401 |
| NCI-H322M | 41310-D| NSCLC      | 0701       | 0202       | 0401        |
| NCI-H460  | 41313-D| NSCLC      | 01a, 04a   | 030101, 050101| N.R.        |
| NCI-H522  | 41314-D| NSCLC      | 040101, 150101| 03a, 0602 | 0401        |
| IGROV1    | 41322-D| Ovarian CA | 11a, 11a   | 03new      | new, 0501   |
| OVCAR-3   | 41323-D| Ovarian CA | 080101, 080401| 0402     | 020102, 0401 |
| OVCAR-4   | 41324-D| Ovarian CA | 030101, 040101| 0201, 030101| 0401, 1301  |
| OVCAR-5   | 41325-D| Ovarian CA | 030101, 040101| 0201, 030101| 0401        |
| OVCAR-8   | 41326-D| Ovarian CA | 0701, 150101| 030302, 0602| 020102, 1301 |
| NCI/ADR-RES| 41295-D| Ovarian CA | 0701, 150101| 030302, 0602| 020102, 1301 |
| SK-OV-3   | 41327-D| Ovarian CA | 01a, 030101| 0201, 050101| 020102, 0401 |
| DU-145    | 41328-D| Prostate CA| N.R.       | 030302, 050101| 0401        |
| PC-3      | 41329-D| Prostate CA| 0701, 130101| 0202, 0603  | 0401        |
HLA-C alleleSEQR Sequenced Based Typing Kits (Atria Genetics, Hayward, CA, U.S.A.). The primary amplification PCR products were purified from excess primers, dNTPs and genomic DNA using ExoSAP-IT (American Life Science, Cleveland, OH, U.S.A.). Each template was sequenced in the forward and reverse sequence orientation for exon 2 and exon 3 according to protocols supplied with the SBT kits. Excess dye terminators were removed from the sequencing products utilizing an ethanol precipitation method with absolute ethanol. The reaction products were reconstituted with 15 µl of Hi-Di™ Formamide (PE Applied Biosystems / Perkin-Elmer, Foster City, CA, U.S.A.) and analyzed on the ABI Prism* 3700 DNA Analyzer with Dye Set file: Z and mobility file: DT3700POP6 [ET].

**Table 3: Sequence-based typing of NCI-60 HLA class II Loci (Continued)**

| Reference | Description |
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