Review Article
Biological basis of cancer health disparities: resources and challenges for research

Sachin K Deshmukh[1*], Shafquat Azim[1*], Aamir Ahmad[1], Haseeb Zubair[1], Nikhil Tyagi[1], Sanjeev K Srivastava[1,2], Arun Bhardwaj[1], Seema Singh[1,3], Rodney P Rocconi[4], Ajay P Singh[1,3]

Departments of [1]Oncologic Sciences, [4]Interdisciplinary Clinical Oncology, Mitchell Cancer Institute, University of South Alabama, Mobile, Alabama 36604, USA; [2]Division of Cell Biology and Genetics, Tatva Biosciences, Coastal Innovation Hub, 600 Clinic Drive, 3rd Floor, Mobile, Alabama 36688, USA; [3]Department of Biochemistry and Molecular Biology, College of Medicine, University of South Alabama, Mobile, Alabama 36688, USA. *Equal contributors.

Abstract: Last few decades have witnessed remarkable progress in our understanding of cancer initiation and progression leading to refinement of prevention and treatment approaches. Although these advances have improved the survival of cancer patients in general, certain racial/ethnic groups have benefited only partially. Footprints of cancer-associated racial disparities are very much evident in cancers of the prostate, breast, cervical, colorectal, endometrium, liver and lung. These health inequalities are mostly attributed to socioeconomic differences among races, but there is a growing realization that these may actually be due to inherent biological differences as well. Indeed, significant data now exist to support the biological basis of racial disparities in cancer, warranting basic research investigations, using appropriate tools and model systems. In this article, we have aimed to succinctly review the literature supporting the biological bases of racial disparities in cancer, along with available resources, databases and model systems that will be of interest to researchers. Moreover, we have highlighted the specific areas that need attention in terms of development of resources and/or tools, and discuss the opportunities and challenges in basic biological research in cancer health disparities.

Keywords: Racial disparity, cell line model, PDX, biobanks, web-based databanks

Cancer health disparities: an overview

Cancer is the second leading cause of deaths in the United States, and is soon expected to surpass heart diseases to become the number one killer disease [1]. A closer look at cancer statistics indicates that certain racial groups are affected disproportionately with regard to cancer incidence, age of onset, aggressiveness and mortality. Although cancer health disparities are observed among several races and ethnic groups, these are most thoroughly investigated between African American (AA) and Caucasian Americans/European American (CA/EA) populations (**Table 1**). Increase in the efforts to generate cancer awareness and provide access to healthcare to enable cancer screening, and thus timely diagnosis and treatment, has not proven enough to reduce the widening gaps in cancer incidence and mortality among racial

groups [2, 3]. This has supported a notion that there is more to underlying causes of cancer health disparities besides just the socioeconomic factors including poverty, limited access to healthcare, lack of health insurance, lack of transportation, poor health literacy, under-use of screening, inconsistency in follow-up and differences in behavior and culture [2, 4]. Indeed, emerging data now suggest that biological factors such as differences at the genetic and epigenetic levels can be crucial for racial inequalities in cancer incidence and clinical outcomes [5, 6]. This recognition has pushed basic research to establish and precisely understand the involved biological mechanisms, and characterize associated factors, so that appropriate and more effective strategies can be planned to deal with. As a result, some new knowledge has evolved along with development of research tools and resources to help with the develop-

Table 1. Age-adjusted cancer-associated mortality rate of African Americans (AA) vs. Caucasian Americans (CA) population in the US from the surveillance, epidemiology and end results-9 (SEER-9) database for 2013. Rates are represented per 100,000 and age-adjusted to the 2000 US population

Cancer Site	Female			Male			Both		
	AA	CA	Disparity Ratio (%)	AA	CA	Disparity Ratio (%)	AA	CA	Disparity Ratio (%)
All sites	158.42	139.68	13.41	240.0	195.69	18.46	189.54	163.34	13.87
Breast	28.19	20.26	39.14						
Colon and Rectum	15.97	11.86	34.65	24.78	16.86	46.97	19.28	14.12	36.54
Corpus and Uterus NOS	8.29	4.30	92.7						
Liver and Intrahepatic Bile Duct	4.26	3.63	17.35	13.44	8.78	53.07	8.38	6.02	39.20
Lung and Bronchus	34.10	36.61	-12.04	65.93	53.84	22.45	46.92	44.09	6.41
Prostate				39.05	17.87	118.52			

ment of novel research hypotheses and execution of investigations. However, such information is staggered and not readily visible for someone wanting to initiate or expand basic research in cancer health disparities. In this review, we have summarized and discussed the evidence that supports the biological basis of racial disparities in cancer. We have also compiled a list of available resources and tools, which we believe will be appreciated by researchers.

Molecular basis of cancer health disparities

Results from epidemiological studies suggest that a number of factors are responsible for cancer-associated health inequalities. While the most emphasis is placed on socioeconomic factors, recent findings strongly argue in favor of the significant participation of biological factors [5, 7]. In this section, we discuss research findings that have indicated involvement of various biological factors in cancer health disparities.

Prostate cancer disparity

Prostate cancer (PC) is the second leading cause of cancer-related deaths in American men; it also exhibits the most prominent racial disparity [8]. The data from various studies suggest that hormones and their receptors may be involved in the manifestation of racial disparity, more specifically in cancers that are hormone-dependent, including PC [9, 10]. Elevated levels of circulating active form of estrogen, 17β-estradiol, implicated in increased risk of prostate cancer [11], have been reported in AA than CA men [12]. Moreover, the data from

immunohistochemical (IHC) staining of PC tissues have also revealed higher expression of ERβ in AA men relative to their CA counterparts [13]. While studying the correlation of prostate-specific antigen (PSA) with tumor size and volume in AA and CA patients, Moul JW *et al.* observed elevated PSA levels across AA patients of all ages, stages and grades of tumor [14]. Of note, AA men with newly diagnosed localized PC also exhibited elevated levels of PSA in serum [15]. In another study, IHC analysis of androgen receptor (AR) in benign and malignant prostate tissues demonstrated 22% higher AR expression in benign samples and 81% higher expression in malignant tissues obtained from AA patients, compared to tissues from CA patients [16]. Correlative epidemiological studies have implicated selenium deficiency in a number of chronic diseases, including cancer [17]. Selenium is documented to have an inverse relation with PC risk [18]. Therefore, observed higher serum selenium content in CA, compared to AA, may possibly explain the reduced PC in CA. In addition to the individual factors studied for their role in PC racial disparity, several investigations have also looked at the molecular signatures for the biological basis of disparity. For example, gene expression profiles of primary prostate tumors resected from AA and CA patients revealed differential expression of genes associated with growth, epithelial-mesenchymal transition (EMT) and metastasis.

Breast cancer disparity

Breast cancer (BC) is the second leading cause of cancer-related deaths in women in the United States [8]. Elevated levels of inflammatory cyto-

kines have been proposed as prognostic factors for BC [19]. These cytokines have also been implicated in BC racial disparity, as the expression of pro-inflammatory cytokines such as resistin and interleukin 6 (IL-6) was found to be significantly high in serum sample of AA, compared to CA BC patients, and the level of resistin was found to correlate with the expression of IL-6 [20]. Interestingly, cell line derived from AA BC patient (MDA-MB-468) also exhibited higher growth and aggressiveness compared to CA cell line (MDA-MB-231) after resistin treatment, likely due to greater expression of its receptor adenylyl cyclase-associated protein 1 (CAP1) [20]. This was the first report implicating resistin and IL-6 in BC racial disparity, even though their role in BC risk has been reported previously [21-23]. Several studies have shown differential level of polymorphisms in IFN-γ and IL-6 in CA vs AA women [24, 25]. Pro-inflammatory cytokines, IFN-γ and IL-6 are crucial in nursing chronic inflammation and have been implicated in tumor growth and metastasis [26]. Interestingly, significant differences were noted in IL-6 and IFN-γ levels between healthy CA and AA women after controlling relevant covariates [27]. Further, DNA methylation and gene expression profiling performed in histologically normal breast tissues of healthy women indicated 282 hypermethylated CpG islands in AAs, compared to 203 hypermethylated CpGs in healthy CA women. These differentially-methylated CpGs were associated with cell death, survival and cell-to-cell signaling [28], indicating a contribution of differentially-expressed cytokines and genetic factors in BC racial disparities. Similar to the studies in PC discussed above that looked at molecular signatures for the biological basis of racial disparity, a number of such studies have been conducted in BC as well. For instance, a comprehensive gene-expression analysis identified a number of differentially-expressed genes in AA vs CA primary BC tumors.

Colorectal cancer disparity

Colorectal cancer (CRC) is the third most common cause of cancer-related deaths in the United States, with more than 102,000 new diagnoses every year [29]. Analysis of total genome methylation and dysregulation of gene expression from AA malignant colon tissues detected 1,588 hypermethylated and 100 hypomethylated regions. Whereas, DNA from the tumor of CA CRC patients showed 109 hypermethylated and 4 hypomethylated regions, indicating 14.6 and 25 fold changes relative to AA [30]. In this analysis, anti-inflammatory genes such as NELL1, GDF1, ARHGEF4, and ITGA4, and miRNAs including miR-9-3p and miR-124-3p (known for their significant role in CRC) were found to be hypermethylated in tumors from AA patients [30]. RNAseq data of this study further revealed upregulation of 34 genes, including Cytochrome P450 1B1 (CYP1B1) in AA CRC patients, compared to CA patients. CYP1B1 metabolizes the exogenous and endogenous compounds into carcinogenic derivatives [31]. Further, it is shown to promote the metabolism of several chemo-therapeutic drugs, including 5-fluorouracil, vincristine, vinblastine, etoposide and cyclophosphamide [32]. The gene expression profiling of CRC samples identified differential expression of genes in AA vs. CA patients.

Endometrial cancer disparity

Endometrial cancer (EC) is the fourth most commonly diagnosed cancer among women in the United States [8]. It is also referred to as the cancer of the uterine corpus as majority of tumors develop in the endometrium, which is the lining of the uterus. Several studies have identified distinct molecular signatures in AA vs CA EC. Gene mutation analysis of EC frozen tissues suggested an association of mutated p53 overexpression with poor clinical outcome, which was a more frequent occurrence in AA, as compared to CA, in both early- (34% vs 11%, respectively) and advanced-stage (55% vs 25%, respectively) patients [33-35]. Specific haplotype (PTEN/10q), found to be significantly different in CA and AA women diagnosed with EC, has been linked with unfavorable outcome [34]. A study on uterine serous papillary endometrial cancer, a highly aggressive variant of EC, identified more frequent overexpression of HER2/neu oncogene in AA patients, compared to their CA counterparts.

Other cancers

Liver cancer (LC) is the fifth most common cause of cancer-related deaths in males, and eighth in females, in the United States [8]. Hepatitis C virus (HCV)-induced hepatocellular carcinoma (HCC) is believed to be a major contributor to higher incidence and mortality of LC

Table 2. Repositories of ethnically diverse biospecimens*

S. No	Repositories of biospecimens	
	Name	Website
1	Cooperative Human Tissue Network	http://www.chtn.org
2	Trans-Hit Biomarker	http://www.trans-hit.com
3	Tissue For Research	http://www.tissue4research.com
4	Gundersen Foundation Biobank	http://www.gundersenhealth.org/biobank
5	Cureline	http://www.cureline.com
6	Cell & Co. Biorepository	http://www.cell-and-co.com
7	American Type Culture Collection	http://www.atcc.org

*This non-exhaustive table lists representative repositories for biospecimens, which the researchers can contact as the starting points for their research needs.

in AA than other ethnic groups in the United States [36]. A proteomic analysis of liver tissues from HCV+/HCC+ patients identified 7-fold differential expression of Apolipoprotein A1 (APOA1) in AA HCC, as compared to CA HCC. Further, hepatocyte nuclear factor4α (HNF4α) protein was found to be downregulated in AA, as compared to CA [37], and lower levels of HNF4α were detected in metastatic HCCs [38]. Reduced HNF4α expression correlates with aggressive clinico-pathological characteristics of HCC, and predicts poor prognosis [39]. Furthermore, AA non-small cell lung cancer (NSCLC) patients have higher circulating levels of IL-1β, interleukin-10 (IL-10) and tumor necrosis factor-α (TNF-α), as compared to CA patients [40]. Moreover, differential expression of these cytokines is found to be associated with lung cancer in AA [40]. Finally, a population-based case-control study of ovarian cancers (OC) linked short CAG repeat length with increased OC risk in AA patients [41].

Available resources to investigate molecular basis of cancer health disparities

The preceding section provided evidence for potential biological basis of cancer racial disparities in different human cancers. While these evidences strongly support biological basis of cancer racial disparity, this knowledge is just emerging. A challenge that the researchers face is the availability of resources to perform innovative research connecting cancer health disparity with their biological causes. Clearly, available resources from published studies as well as clinical resources from racially diverse groups can be immensely helpful in furthering innovative research in cancer health disparities towards identifying novel molecular distinctions among racially diverse groups of patients.

Repositories of biospecimens

Biobanks are repositories of biological specimens, usually derived from humans, and collected under specified guidelines for patient consent and enrollment, specimen collection, processing, annotation, storage and distribution. Many different kinds of biobanks are available these days that range from federally-supported to University-based to even ones that are purely commercial. Biorepositories have contributed to cancer research by lowering the cost and increasing the pace of research. Specimens can be shared by many projects and hence minimize the concerns about cohort size. The type of biospecimens include frozen tissues, formalin-fixed paraffin-embedded tissues, fresh tissues, blood or blood products, ascites/peritoneal fluid, urine, saliva, isolated cells, DNA and protein from both normal and tumor patients. These samples are of great significance in medical research and support studies related to genomics, personalized medicine and racial disparity. Nearly all major cancer institutes in the United States maintain their own biobanks, from which samples are available to researchers upon request, with some associated costs. It is beyond the scope of this article to list the hundreds of available biobank/biorepositories; however we have listed some prominent university/institutional based repositories of specimens in **Table 2**. Specimens belonging to different ethnicities can usually be obtained from these biobanks helping researchers unveil the mechanism of racial disparity in different types of cancers. Furthermore, the development and organiza-

Table 3. List of web-based databanks*

S. No	Databank	
	Name	Website
1	The Cancer Genome Atlas	http://cancergenome.nih.gov
2	International Cancer Genome Consortium	http://icgc.org
3	Catalogue of Somatic Mutation in Cancer	http://cancer.sanger.ac.uk/cosmic
4	Collaborative Cancer Cell Line Encyclopedia	http://www.broadinstitute.org/ccle
5	Myriad	http://www.myriadtests.com
6	Peptide Atlas	http://www.peptideatlas.org
7	Global Proteome Machine Database	http://gpmdb.thegpm.org
8	Tranche	http://www.tranche.proteomecommons.org
9	PRIDE Proteomics Identification	http://www.ebi.ac.uk/pride/
10	Human Proteinpedia	http://www.humanproteinpedia.org
11	Yeast Resource Center	http://depts.washington.edu/yeastrc

*This non-exhaustive list provides information on some of the prominent databanks that can serve as excellent starting points for interested researchers.

tion of such biobanks has facilitated extensive collaborative efforts between research groups from around the globe [42].

Web-based databanks

The advancement of experimental technologies and integration of computational sciences in biology has aided in the significant strides being made to understand the molecular basis of diseases, particularly cancer. Furthermore, with the development of modern sequencing platforms, the cost of sequencing has considerably decreased, generating enormous data and minute details to quantify gene expression, miRNA expression and identification of alternative splicing events. Mass Spectrometry has also been employed to generate significant proteomics data comparing CA and AA tumors and several proteomics repositories have been setup to store and share the information generated. On similar lines, differences in the metabolome of CA and AA patients are also being explored to understand the altered onco-metabolic pathways. However, a publicly available repository for metabolomics studies is still lacking. A non-exhaustive list of databanks is presented in **Table 3**.

Novel and established models expediting cancer health disparities research

Suggested biological basis of racial disparity needs to be investigated further to establish cause-effect relationship. Moreover, involved molecular mechanisms need to be pinned down further to help in the planning of effective strategies to reduce the disparity gaps. The recruitment of patients for exploratory experimentation is restricted by ethical and safety issues. Hence, it is crucial to develop appropriate model systems to help understand molecular and biological basis of racial disparity, so that advancements could be made in cancer prevention and therapy. The routinely used laboratory models in cancer research include established cancer cell lines, xenograft-mouse models and genetically-engineered spontaneous progression mouse models. In this section, we discuss the importance of these model systems and provide information on commercially available cell lines from distinct ethnic backgrounds that can be utilized in disparity-focused research. We further advocate the need of new cell lines along with the generation of patient-derived xenografts or orthotropic mouse models.

Cancer cell lines for in vitro research

Patient-derived cancer cell lines have emerged as important models and invaluable tools in cancer research. Racial disparity in cancer is manifested in the form of incidences, aggressiveness, mortality as well as drug-resistance [43]. Cancer cell lines are routinely used as the first-line models to test drug potency [44-46]. Since the cell lines derived from different patients recapitulate the genetic background of the individual tumors, they serve as excellent tools to study the genetic and epigenetic differences. Further, the use of cell lines of diverse

Table 4. Comprehensive list of cell lines derived from patients of different racial backgrounds

Cancer	Race	Cell lines
Breast cancer	CA	AU565, BT-20$^{\pm}$, BT-474, BT-549$^{\pm}$, CAMA-1, DU4475$^{\pm}$, HCC38$^{\pm}$, HCC202, HCC1143$^{\pm}$, HCC1187$^{\pm}$, HCC1395$^{\pm}$, HCC1428, HCC1599$^{\pm}$, HCC1937, HCC2218, Hs 578T$^{\pm}$, MCF7, MCF 10A, MCF-12A, MDA-kb2, MDA-MB-134-VI, MDA-MB-231$^{\pm}$, MDA-MB-361, MDA-MB-436$^{\pm}$, MDA-MB-453$^{\pm}$, SK-BR-3, UACC-893, ZR-75-1
	AA	HCC70$^{\pm}$, HCC1500, HCC1569, HCC1806$^{\pm}$, HCC2157, MDA-MB-157$^{\pm}$, MDA-MB-175-VII, MDA-MB-468$^{\pm}$, ZR-75-30
Colorectal cancer	CA	SK-CO-1$^{\sim}$, SW1116, SW948, LS123, SW837, SW48, COLO 205$^{\sim}$, SW1417, LS411N, NCI-H508, HT-29, WiDr, LS 174T, DLD-1, LS1034, SW480, SW620$^{\sim}$
	AA	NONE
Cervical cancer	CA	Hs 588.T, C-4 I, C-4 II, C-33 A
	AA	HeLa, HeLa 229, HeLa S3, H1HeLa, HeLaRC32
	Asian	SiHa
Ovarian cancer	CA	Caov-3, UACC-2727, OVCAR-3, TOV-112D, TOV-21G, SKOV-3, OV-90$^{\sim}$, Caov-4, SW 626, PA-1
	AA	ES-2$^{\#}$
Uterus and endometrial cancer	CA	SK-UT-1, SK-UT-1B, MES-SA$^{\#}$, MES-SA/MX2$^{\#}$, KLE, RL95-2, AN3 CA
	AA	None
Liver cancer	CA	C3A, HEP G2/2.2.1, Hep G2/HB-8065
	AA	Hep 3B2.1-7
	Asian	SNU-449, SNU-475, SNU-387, SNU-398
Prostate cancer	CA	DU 145$^{\sim}$, PC3$^{\sim}$, LNCaP clone FGC$^{*,\sim}$, CA-HPV-10, DuCaP$^{*,\sim}$, RC-92a/hTERT, RC-170N/hTERT, RC-165N/hTERT^{+}
	AA	E006AA-hT*, E006AA*, MDA PCa 2b$^{+,\sim}$, S006AA*, RC-77N/E^{+}, RC-77T/E^{+}
Lung cancer	CA	NCI-H838$^{\sim}$, HCC827, SK-LU-1, HCC2935, HCC4006$^{\sim}$, NCI-H1819$^{\sim}$, NCI-H676B$^{\sim}$, Calu-3$^{\sim}$, Hs 618.T$^{\#}$, HBE4-E6/E7, NCI-H1666$^{\sim}$, NCI-H1568, NCI-H2126$^{\sim}$, NCI-H596, SW 1573, MSTO-211H$^{\#,\sim}$, Hs 573.T$^{\#}$, Hs 573.Lu$^{\#}$, NCI-H727, A549, A-427, A549, NCI-H1688$^{\sim}$, NCI-H187$^{\sim}$, NCI-H661$^{\sim}$, NCI-H1299$^{\sim}$, NCI-H1155$^{\sim}$, DMS 114, NCI-H69, DMS 79, DMS 53, SW 1271, SHP-77, NCI-H209$^{\sim}$, NCI-H146$^{\sim}$, NCI-H345$^{\sim}$, DMS 153, NCI-H82$^{\sim}$, NCI-H446$^{\sim}$, NCI-H510A$^{\sim}$, H69AR, Calu-1$^{\sim}$, SW 900, NCI-H1703, SK-MES-1$^{\sim}$, NCI-H2347, NCI-H2087$^{\sim}$, NCI-H1437$^{\sim}$, NCI-H2066, DMS 153, H2286, H1395, H522, H2073, H2342, H1993, H2023, H647, H1623, H1944, H1650, H1781, H1693, H1792, H2009, H1355, H1573, H2405, H1755, H920, H2122, H1770, H1581, H2106, H1869, H1915$^{\sim}$, H889, H1417, H1694, H719, H1092, H740, H1105, H1436, H1876, H378, H2081, H774, H711, H2227, H211, H1238, H1618, H1882, H2195, H2196, H2029, H2141, H2198, H2171, H735$^{\sim}$, H64, H526, H196, H1672, H1836, H1930, H865, H847, H1963, H1184, H2330, H524, H841
	AA	NCI-H23, NCI-H835, CCD-13Lu$^{\#}$, NCI-H128$^{\sim}$, HLF-a$^{\#}$, NCI-H292, H810, H1648, H1385, H250, H748, H220, H2107, H2108

*(androgen dependent), $^{+}$(androgen sensitive), $^{\#}$(fibroblast), $^{\pm}$(triple negative), $^{\sim}$(derived from metastatic site), S006AA is prostate cancer associated stromal cells.

genetic background brings substantial weightage to the understanding of signaling pathways pertaining to a particular therapeutic response. In addition, cell lines facilitate the repetition of experiment on genetically identical cells, which cannot be substituted by primary cell lines obtained from multiple tissue donors. Another advantage of cell lines is that they provide a unique opportunity to manipulate the genetic content, which allows functional characterization of genes and their signaling network(s) pertaining to their roles in disease pathobiology.

Although animal models, wherever available, are the most appropriate model systems for research, their use in certain studies including manipulations for the genetic and epigenetic analyses is difficult to practice. Under these circumstances, cell lines serve as a feasible alternative. They are easy to manipulate and molecularly characterize, and also address the potential ethical concerns [47]. The exceptional benefits of cell culture, such as, continuous supply of live cells and controllable experimental factors, have proven to be helpful in determining the major player(s) of differential tumor progression in diverse ethnic groups [47].

Considering the importance of *in vitro* model systems, significant efforts have been devoted for the establishment of cell lines from cancer patients. This endeavor resulted in development of several cell lines, although unintentionally, derived from racially disparate cancers (**Table 4**). These cell lines represent an excellent resource for continuing mechanistic studies on biological basis of cancer disparity, but there clearly is need for the development of more immortal cell lines for specific racial groups. Cell lines derived from different ethnic background can be helpful in understanding the biological factors that lead to adverse clinical outcome in a particular race.

Although the section above on racial disparity in individual cancers briefly describes a few studies that have employed cell line models to understand cancer racial disparity, additionally, it has been demonstrated that the racial differences in BC might even exist at the level of cancer stem cells (CSCs). Breast CSCs isolated from AA cell lines, CRL-2335 and MDA-MB-468, showed significantly longer survival and greater ability to develop mammospheres, compared to those from CA triple-negative breast cancer (TNBC) cell lines, BT549 and MDA-MB-231. Further, treatment with cisplatin plus TNF-related apoptosis-inducing ligand (TRAIL) decreased expression of miR-23b and miR-100 and significantly increased FZD8, a Wnt receptor crucial for CSC renewal, more profoundly in AA cell lines, as compared to CA cell lines [48, 49]. The CSCs are believed to be involved in the initiation and progression of many malignancies, including CRC [50-52]. Another independent study suggested that the number of adenomas, which is significantly higher (48%) in AA, is associated with 50-80% higher CSC sig-
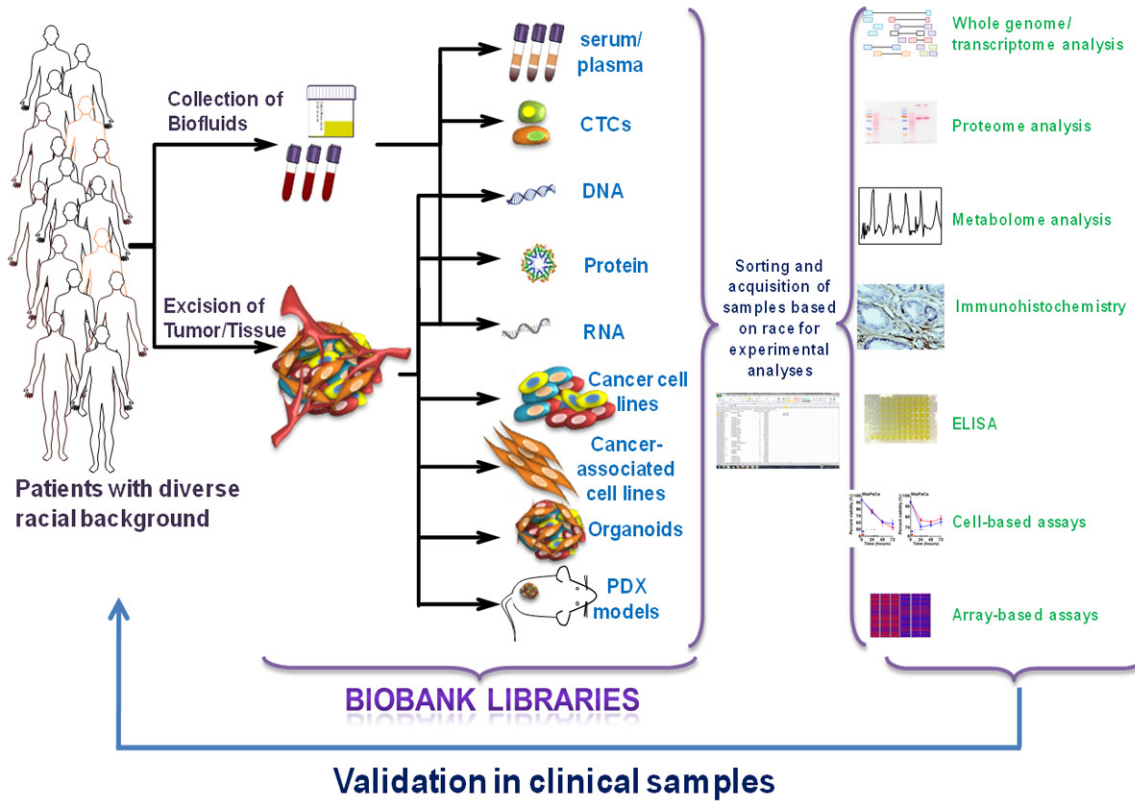
nature, CD44$^+$ CD166$^-$, in the colonic effluent and colonic mucosa from AA, compared to CA patients [53].

The studies described above are good examples of how investigations using cell lines have led the way in understanding the biological basis of cancer racial disparity. These studies have played a key role in re-enforcing the biological basis of racial disparity. A pubmed search in October 2016 for literature with the keywords 'cancer cell line' returned 1,83,004 articles, highlighting the importance of cancer cell lines in cancer research. However, when searched for 'racial disparity and cancer cell line' only 6 publications were retrieved, suggesting that this system has not been exploited much in the study of the racial disparity. This may be partly due to unavailability of cancer cell lines derived from different ethnic backgrounds. In order to study racial disparity in cancers such as prostate and breast, we do have available cell lines of AA vs CA origin, however, as is obvious from the list of cell lines (**Table 4**), there remains an urgent need to develop and establish cell lines for colorectal, uterus and endometrial cancers of AA background. Racial disparity is prominent in these cancers with a disparity ratio of 36.54% for both sexes in CRC and 92.7% for females in uterus and EC (**Table 1**). The availability of cell lines from different ethnic backgrounds will help us elucidate the mechanisms and signaling pathways behind the disparity. Therefore, in such circumstances it is practically difficult to determine the molecular differences between CA and AA ethnic background *in vitro.*

Translational model with clinical implications: patients-derived xenografts

Tumor heterogeneity poses one of the biggest challenges in development of effective cancer therapeutics and has led to use of a newer type of tumor model i.e. Patients-Derived Xenograft (PDX). PDX models are created by transplanting tissues from patients' primary tumors directly into immunodeficient mice and thus reflect the biological characteristics of human tumors more accurately than cell line-derived xenografts. PDX models are being used in pre-clinical research to test the efficacy of newer drugs due to their closer similarity with tumor in terms of tumor heterogeneity, tumor architecture as

Figure 1. Tools to study cancer racial disparity. Patient derived samples; such as body fluids, excised tumor or biopsy tissue, from cohorts of diverse ethnic backgrounds are collected and maintained by biobanks/biorepositories. Biofluids can be used to isolate circulating tumor cells (CTCs), DNA, RNA, protein, which can be processed further *in vitro* to identify potential biological factors associated with disparity. Excised tumor or biopsy tissue can be the source of DNA, RNA, protein, cancer cell lines, cancer-associated tumor microenvironment cells, organoid culture and patient-derived xenografts (PDX) engraftment. The samples available from different Institutional/commercial biobanks can be sorted and acquired for detailed investigations. Samples can be subjected to detailed molecular/functional profiling and/or arrays in the search for novel factors underlining the biological basis of cancer racial disparity. As a final step that completes the loop, any novel findings can be validated in clinical samples from biobanks.

well as tumor microenvironment [54, 55]. Since the TME is implicated in tumor aggressiveness, drug resistance as well as in response to therapy, PDX models are now widely employed to study tumor heterogeneity, therapeutic target validation, and sensitivity and resistance to therapy [56]. They also mimic human clinical trials and are useful tools for testing the drugs or combinations of drugs prior to their actual testing in human patients [56, 57].

To study the drug responses in racially disparate BC, AA and CA PDX models have been generated [52, 58]. Azizi *et al*. generated PDX models utilizing tissues from various ethnic groups. Gene expression was analyzed in single cells and, interestingly, significant differences were observed in the expression of cancer-associated genes between each ethic group of BC PDX

samples [59]. These PDX models revealed differential expression of genes such as Vimentin, EpCAM, HER2, CDH1, CDH2, TGFβ1, cytokeratins, GATA3 and MKI67, which are associated with EMT phenotype. In addition, differences in the expression of genes such as YAP1, TM4SF1, TSPAN6, AMOTL2, STAP2 and ANXA3 were also detected in the PDX samples. Furthermore, CSC markers ALDH1a1, ALDH1a3, CD44, CD24, and CD133 were found to be differentially-expressed in different PDX single cell samples. In pancreatic carcinoma, the orthotopic implantation more accurately predicted a patient's response to chemotherapy than those models where implantation was done at a heterologous site [60]. Considering the advantages of PDX models in clinical trials, a Public Repository of Xenografts has been generated by orthotopic implantation of well-character-

ized leukemia and lymphoma (PRoXe, http://www.proxe.org).

Perspectives and future direction

Although the non-biological factors have long been held responsible for the observed racial disparities in cancer incidence and/or clinical outcome, recent years have witnessed a growing realization for the biological basis of cancer racial disparity. This has led to hunt for appropriate resources and models for a meaningful research. Here, we have provided a comprehensive overview and assessment of the available resources and tools that can potentially be utilized to explore the biological basis of health disparities in cancer (**Figure 1**). More than anywhere else, research on cancer health disparity relies heavily on available specimens from patients representing distinct racial backgrounds. As pointed out, a number of biobanks and repositories are available, almost at every major institution, and several that are either developed through federal funds or for commercial purposes. With each repository being maintained individually, it warrants a major ground work to identify and procure specimens of interest. An integration of all such repositories or the possibility of a search engine with filtering capabilities would be a dream-come-true for researchers in the field. The endless possibilities that these specimens can be subjected to, from arrays to systemic profiling, has helped generate enormous data which, even when aided by numerous analyses software/platforms, is still overwhelming at times.

Both *in vitro* and *in vivo* models have their utility in cancer racial disparity research. With their versatility, ease of handling and possibility of genetic/molecular modifications, cell line-based models have become an important tool in the validation and mechanistic studies. Appropriate cell line(s) can be selected to improve current understanding of racial disparity, which can further lead to the development and testing of novel therapeutics to ultimately reduce the disparity gaps in clinical outcomes. However, as identified above, there is need for the development of AA cell lines representing individual cancers. With the increase in Hispanic and Asian populations in the US, and the realization that these populations might also have disparate cancer incidence and mortality, at least for a few specific cancers, the need for

cell lines representing these 'new' population groups has also suddenly sprung. Understanding gained by the use of several resources; primary tumors, xenografts, paraffin-embedded samples, genetically-engineered mice and cancer cell lines, has opened uncharted territory of therapeutics to counter cancer. The same resources are being utilized for cancer racial disparity research, which has necessitated adaptation of these resources to fit the unique needs and requirements of research focused on cancer racial disparity. Last several years of efforts have resulted in development and/or adaptation of several resources to serve the needs of racial disparity research and this is predicted to continue, given the general increased interest in the research topic and the increased federal funding supporting such investigations.

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Disclosure of conflict of interest

APS and SS are co-founders, and serve on executive management team of Tatva Biosciences LLC, which is involved in the development of tools and models for cancer health disparity research. SKS serves as the Director of Cell Biology and Genetics at Tatva Biosciences LLC.

Address correspondence to: Dr. Ajay P Singh, Department of Oncologic Sciences, Mitchell Cancer Institute, University of South Alabama, 1660 Springhill Avenue, Mobile, Alabama 36604-1405, USA. Tel: 251-445-9843; Fax: 251-460-6994; E-mail: asingh@health.southalabama.edu

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