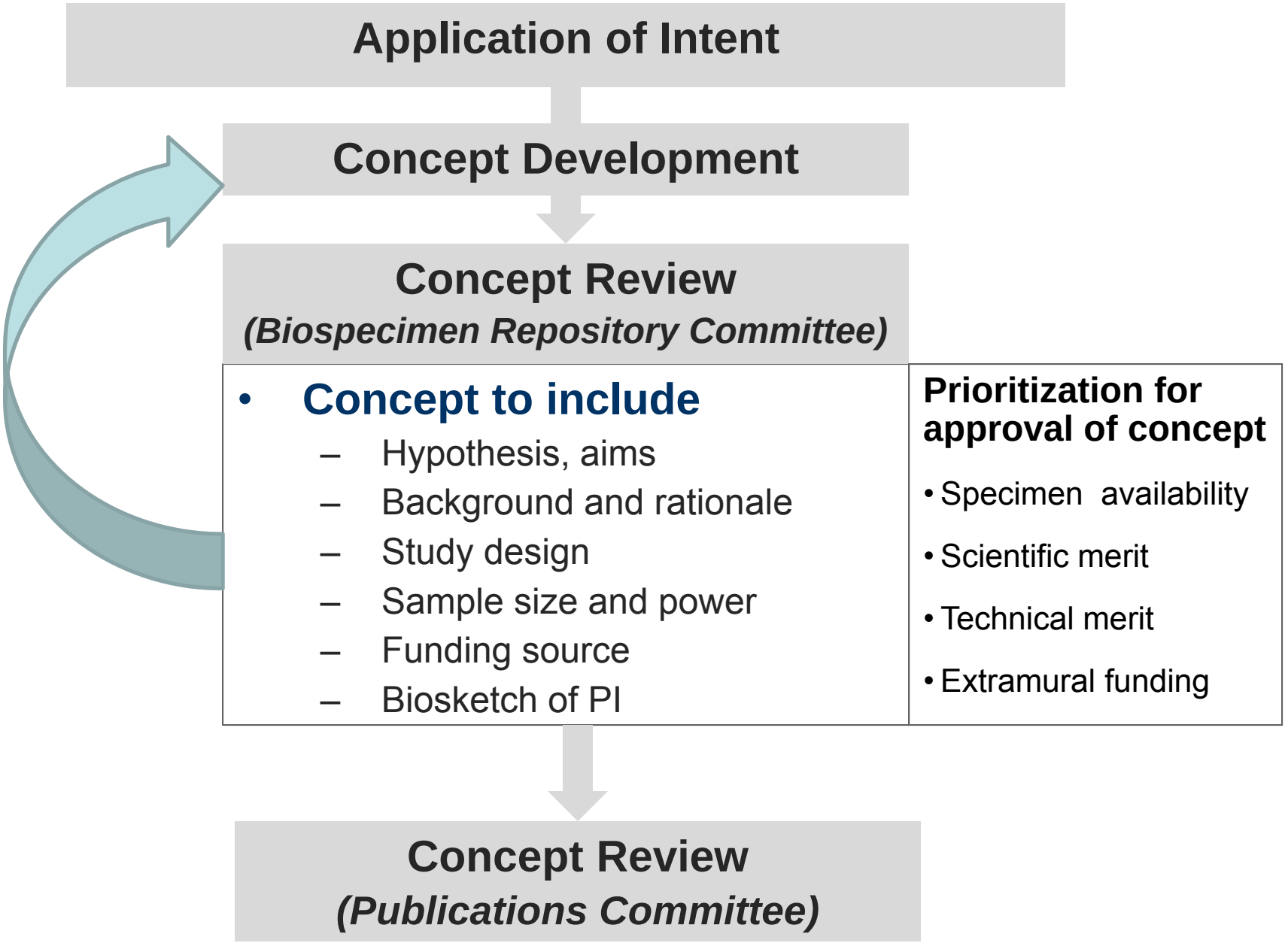
Genetics Working Group

Concepts/ AOIs

June, 2012

Process for biospecimen acquisition



Concept # 1	**Genomic alterations in radiation-related breast cancer using Array-CGH (Comparative Genomic Hybridization)**
PI	**Rose Yang, NCI**

Genomic alterations in RT-related breast cancer using Array-CGH

Aims

Distinct prevalence/ patterns of DNA CNV?

Distinct genomic aberrations by high-dose (CCSS), low-dose (Lifespan), no radiation?

Distinct genomic aberrations by age at exposure and acute vs. protracted exposures?

Results

Typical breast cancer CGH profile observed;

changes do not correlate with radiation exposure

tumor ER, Ki67 stain correlate CGH data with tumor subtype and proliferation

Status

Identified age-matched reference population

Writing up the findings for a publication

Concept # 2	Evaluation of SNPs in the EWS Breakpoint Region in People with/ without Ewing sarcoma
PI	Stephen DuBois, UCSF

Evaluation of SNPs in the EWS Breakpoint Region in People with and without Ewing sarcoma

Primary Aim

Case control study: Ewings sarcoma, controls

18 tagged HapMap SNPs span entire *EWSR1* gene

Secondary Aims

Compare frequency of SNPs in the *EWSR1* gene between

- Ewing Sarc 5 yr survivors with non-survivors
- Ewing sarcoma patients with siblings
- SNPs associated with Ewing sarcoma in a control population of African ancestry

Results

Variations in *EWSR1* at known SNPs or across intron 7 are not associated with Ewing sarcoma

EWSR1 does not appear to be an Ewing sarcoma susceptibility gene

Dubois S et al. Pediatr Blood Cancer, 2011

Concept # 3	**Genetic Susceptibility to Obesity after Childhood Leukemia**
PI	**Kala Kamdar, Baylor**

Aims

GWAS: SNPs and CNVs in 1200 ALL survivors in CCSS

Determine relation tx-related obesity and genotype

Demographic/tx variables as risk modifiers?

Replicate top SNPs/ CNVs from Discovery in independent sample of at least 400 ALL survivors from TCH

Status

Funding procured (LLS)

GWAS analysis planned for this year as part of NCI GWAS initiative

Concept 4

Genetic Epidemiology of Basal Cell Carcinoma in Childhood Cancer Survivors

PI

Stella Davies, Cincinnati

Aims

Identify susceptibility polymorphisms in genes related to radiation sensitivity

Create a prediction model, using gene-environment interaction data for radiation sensitivity

Methods

Matched case control study design

Candidate gene approach

Status

Funding: NIH (U01)

Cases and controls identified (3/10)

Genotyping largely done; Cleaning up data CC

Concept # 5 GWAS of SMNs after Hodgkin lymphoma

PI Ken Onel, U of Chicago

Aims GWAS of Rad-rel SMNs in HL

Design Matched case-control study design

Discovery set: 103 cases with SMNs and 121 controls with no SMNs

Replication set: 120 cases and 112 controls

Funding **NIH (R21)**

Results 2 variants chr 6q21 associated with SMN

- Variants associated with decreased basal *PRDM1* expression, and impaired induction of *PRDM1* by radiation exposure
- Implicates *PRDM1* in the etiology of RT-induced SMNs

PRDM1 involved in proliferation, differentiation, apoptosis

Best T et al, Nat Med 2011;17:941-3

Concept # 6

Telomere length and Second Malignancy in Pediatric Cancer Survivors

PI Monica Gramatges, Baylor

Telomere length/SMN in Pediatric Cancer Survivors

Hypothesis

Shortened germline telomere length plays a role in in SMN in childhood cancer survivors

- increased likelihood for mutational gains/losses in an already strained checkpoint system upon genotoxic exposure

Aims

Investigate telomere length in buccal DNA samples from childhood cancer survivors

Methods

Matched case-control study design qPCR analysis to measure telomere length

Results

Preliminary findings support hypothesis

Plans

Abstract for ASH, ms under preparation

Concept # 7	**Susceptibility genes for radiation-induced breast cancer after Hodgkin lymphoma**
PI	**van Leeuwen/ Netherlands Robison, Bhatia/ CCSS**

Aim GWAS susceptibility rad-related breast cancer after HL

Design Case-control study design:

Cases: Caucasians with HL and RR-breast cancer

Controls: Breast cancer free Caucasians with HL at date of inclusion as controls

Matching criteria: age at dx of HL; calendar yr of HL dx; length of f/u ≥ cases; exposure to supradiaphragmatic radiation

Platform Illumina iSelect 200,000 targeted SNP chip, data on a comparison series of young BC without HL

Status Cases/ controls identified

Samples shipped to NL

Concept # 8 **Genetic susceptibility to anthracycline-related CHF – validation study**

PI **Smita Bhatia, City of Hope**

Genetic susceptibility to anthracycline-related CHF: Validation study

Aims

Verify significant findings identified in the Discovery set (using COG-case-control study [ALTE03N1] in an independent case-control set from CCSS

Status

Concept approved

Cases and controls identified for validation

Samples to be released

Concept # 9 Radiation-related thyroid cancer

PI Yuri Nikiforov, U of Pittsburgh

Radiation-related thyroid cancer

Aim

Test hypothesis that non-random DNA breakages and/or rejoining events play a role in RET/PTC rearrangement after exposure to radiation

Test for alterations in DNA repair genes (*ATM, BLM, NBS1, DNA-PKcs, Ku70, XRCC4, RAD51*) in thyroid cancer patients exposed to radiation

Design

Matched case-control

Matching criteria: Primary diagnosis, radiation field includes thyroid, sex, age at exposure, race/ ethnicity, duration of follow-up to exceed latency between primary diagnosis and thyroid cancer

Status

Cases and controls identified

Samples to be released

Concept # 10 Genetic Alterations in Second Malignant Neoplasms

PI **Jean Nakamura, UCSF**

Genetic Alterations in Second Malignant Neoplasms

Aim 1 Test if LOH in tumor suppressor genes (identified in the *Nf1* mutant mouse model) occurs in SMNs

Taqman-based SNP genotyping on SMN FFPE DNA

Initial analysis focus on 5 most commonly altered TSG genes identified in PI's mouse model

Aim 2 Determine whether transcript levels of candidate tumor suppressor genes are reduced in SMNs

Isolate mRNA from SMN FFPE matched normal and tumor

Perform PCR-based quantitation of candidate TS transcripts

Specimens Unstained, fixed sections of SMN samples Breast (n=48), Meningioma (n=23), CNS (n=18), sarcoma (n=10)

Samples to be released

Concept # 11 Genome-wide Association Study of Subsequent Malignant Neoplasms among Childhood Cancer Survivors (NCI/ CCSS)

Applications of Intent

AOI #1 Genetic Susceptibilities to SMNs (Onel/ U of Chicago)

Specific Aim	Test the association of top SNPs from the GWAS study with risk for second cancers after primary diagnoses other than HL
Eligibility criteria	All patients with SMNs and controls 1:1 matched for primary cancer, latency, age of treatment for primary cancer, treatment modality, gender, and race/ethnicity
Status	Concept is being finalized

AOI #2 PRDM1 and somatic mutations in SMNs after HL (Onel/ U of Chicago)

Specific Aim	Genotype chr 6q21 risk locus in all samples; assess (FISH / IHC) *PRDM1, MYC* mutation status in SMNs
Eligibility criteria	Archival tumor samples of radiation-induced SMNs after HL
Status	Concept is being finalized

AOI #3 Molecular variation between primary breast cancers and radiation-related breast cancer (Pelloski/Ohio State)

Specific Aim	Using gene expression techniques, describe prevalence/ distribution of molecular subclasses (Luminal A, Luminal B, Basal, Her2-enriched and breast-like breast cancer subtypes) in radiation-related breast cancer, compare with *de novo* breast ca
Status	Concept is being finalized