Understanding the Development and Progression of Disease.

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Overview

- Clinical Breast Care Project (CBCP)
- Windber Research Institute
- Data, Information and Knowledge
- Systems Biology
- Defining Translational Research
- Understanding the Question(s)
Clinical Breast Care Project

- Creation of CBCP reference database
  - 10,000 breast disease patients/year
    - Ethnic diversity; “transient
    - Equal access to health care for breast disease
    - All acquired under SINGLE PROTOCOL
    - All reviewed by a SINGLE PATHOLOGIST
  - Tissue, serum, lymph nodes (>14,000 samples)
  - Patient data (500+data fields)
  - Mammograms, 4d-ultrasound, PET/CT, 3T MRI
  - Complementary genomics and proteomics, IHC
  - Breast cancer vaccine program (her2/neu)
Windber Research Institute

- Founded in 2001, 501(c)(3) corporation
- Genomic, proteomic and informatics collaboration with WRAMC
- 45 scientists (8 biomedical informaticians)
- 36,000 sq ft facility under construction
- Focus on Women’s Health, Cardiovascular Disease, Processes of Aging
WRI’s Mission

WRI intends to be a catalyst in the creation of the “next-generation” of medicine, integrating basic and clinical research with an emphasis on improving patient care and the quality of life for the patient and their family.
Systems Biology
(Personalized Medicine)
Bottom Up Approach

- Genomics
- Proteomics
- Metabolomics
- CGH
- Physiology
- Patient
- ????
Top Down Approach (Personalized Disease)
Translational Medicine
“Discovery consists in seeing what Everyone else has seen and thinking What no one else has thought”

A. Szent-Gyorgi
1. Modeling Disease

- Disease as a State vs Disease as a Process
- Bias of Perspective
- Temporal Perspective
Modeling Disease

\[
\{ \text{Risk(s)} \} \quad \text{Lifestyle + Environment} = F(t) \quad \{ \text{Disease(s)} \}
\]

\[\begin{align*}
\text{Genotype} & \quad \text{Phenotype} \\
\text{(SNP’s, Expression Data)} & \quad \text{(Clinical History and Data)}
\end{align*}\]
UMLS Semantic Network
Disease Etiology

Genetic Risk

Lifestyle Factors

Breast Cancer

Survival (Chronic Disease)
Phenotype

Genotype

Childhood Diseases

Smoking

Overweight

Diabetes

Cardiovascular Disease

2nd Hand Smoke

Breast Cancer (Age 48)

Natural History?

Phenotype

TIME
Longitudinal Interactions in Breast Cancer

- Identify Environmental Factors
- Quantify Exposure
  - When?
  - How Long?
  - How Much?
- Extract *Dosing* Model
- Compare with Stages of Biological Development
Lifestyle Factors

Smoking

Obesity

Alcohol
2. Genetics and Disease

- Genetic Pre-Disposition
  - < 10 % of all breast cancers
  - Not all BRCA1 and BRCA2 mutations result in breast cancer
    - Modifier genes?
    - Lifestyle or environmental factors?
    - Pedigree Analysis
Pedigree (modified)

- Influenza Pandemic 1918
- 1940
- 1950
- 1960
- 1970
- 1980
- 1990
- 2000

- Measles
- Polio Vaccine
- Influenza
- Menopause
- PSA
- Prostate Cancer
3. Aging and Disease

- Processes of Aging vs Disease Processes
- Ongoing Breast Development
- Same Disease : Different Host?
- Text Data-mining Approaches
Disease vs Aging

Menarche

Peri-menopause

Child-bearing

Menopause

<50 years

Hormone Replacement

Heart Disease

Breast Cancer

Ovarian Cancer

Osteoporosis

Alzheimer’s

Aging

Disease

Quality of Life
Breast Development

- Cumulative Development
- Menarche
- Lactation
- Child-bearing
- Menopause
- Peri-menopause
Ontology: Breast Development

Parous

Terminal Buds

Buds

Lobes

Ducts

Neo-Menarche

Pregnancy

Lactation

Perimenopausal Menopause

Post-Menopausal Menopause

Nulliparous

Buds

Lobes

Terminal Buds

Human Mouse?
Puberty:

- Two hormones – estrogen and progesterone signal the development of the glandular breast tissue.
- In female estrogen acts on mesenchymal cells to stimulate further development.
- The gland increases in size due to deposition of interlobular fat.
- The ducts extend and branch into the expanding stroma.
- The epithelial cell proliferation and basement membrane remodeling is controlled by interactions between the epithelium and the intra-lobular hormone sensitive zone of fibroblasts.
- The smallest ducts, the intra-lobular ducts, end in the epithelial buds which are the prospective secretory alveoli.
- Breast ducts begin to grow and this growth continues until menstruation begins.

Production of: Stroma, mesenchymal cells, epithelial cells
Reality of Disease

DNA    RNA Amino Acids
Genes
Proteins
Enzymes    Substrates    Co-Factors
Pathways
Tissues    Cells    Organelles

Processes: Tissue generation; Inflammation....

Physiological Systems

Gene Ontology

Physiological Development
(time)

Disease Progression
(time)
4. Stratifying Disease

- Tumor Staging
- T,M,N tumor scoring
- Analysis of Outcomes
Cancer Progression

localized → regional → metastatic

0 I IIA IIB IIIA IIIB IV
Tumor Progression

0  I  IIA  IIIB  IIIA  IV  IIIIB
Tumor Staging

Stage 0
(Tis, N0, M0)

Stage I
(T1,* N0, M0) ; [*T1 includes T1mic]

Stage IIA
(T0, N1, M0) ; (T1,* N1,** M0); (T2, N0, M0) [*T1 includes T1mic ]
[**The prognosis of patients with pN1a disease is similar to that of patients with pN0 disease]

Stage IIB
(T2, N1, M0) ; (T3, N0, M0)

Stage IIIA
(T0, N2, M0); (T1,* N2, M0); (T2, N2, M0); (T3, N1, M0); (T3, N2, M0)
[*T1 includes T1mic ]

Stage IIIB
(T4, Any N, M0) ; (Any T, N3, M0)

Stage IV
(Any T, Any N, M1)

Stage IIIC
(Any T, N3, Any M)

10/10/02
(T, M, N) Information Content
Data Integration

- Data Warehouse Model
  - Teradata ➔ Oracle
- Cimarron’s Scierra LIMS
  - Amersham LWS
- Creation of CLWS
A Patient is:

- Family History…….. Nurse
- Genomics............ Genetic Couns.
- Demographics....... Epidemiologist
- Environment........ Envir. Scientist
- Lifestyle............. Social Scientist
- Clinical History..... Physician
- Therapeutic History.. Pharmacist
- Tissue Samples....... Pathologist
- Cost of Treatment... Insurer
- Quality of Life....... Patient

A Patient is a Mother, Sister, Wife, Daughter.....
Modular Data Model

- Socio-demographics (SD)
- Reproductive History (RH)
- Family History (FH)
- Lifestyle/exposures (LE)
- Clinical history (CH)
- Pathology report (P)
- Tissue/sample repository (T/S)
- Outcomes (O)
- Genomics (G)
- Biomarkers (B)
- Co-morbidities (C)
- Proteomics (Pr)

Swappable based on Disease
Conclusions

- Personalized Disease will improve Patient Care, Today; Personalized Medicine, Tomorrow
- Disease is a Process, not a State
- Translational Medicine must be both:
  - Bedside-to-bench, and
  - Bench-to-bedside
- The processes of aging are critical:
  - For accurate diagnosis of the patient
  - For converting breast cancer to a chronic disease
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Patients, Personnel and Family!
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