Advances in Treatment: What’s on the Horizon

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CANCER AND BIOMEDICAL RESEARCH EXPENSE
Ultimate question is whether to spend money on cure or long-term alleviation of suffering and care of potentially curable patients

• Cons:
  – It takes long time to introduce a drug
  – Uncertain results of medical research
  – Urgent needs to provide care to poor now
  – Need to improve current care

• Pros:
  – New therapies are a fruit of long-term research that needs to be done to achieve progress
  – New development can dramatically change outcomes and saves lives
  – Ultimately the need for chronic, palliative and charitable care would be abolished due to prospect of cure

Through discovery of disease causes (Pathogenesis) and disease mechanisms (Pathophysiology) and thank to the patients willing to participate in clinical trials it is possible to identify rational targets of therapy.

IS IT WISE TO INVEST IN CANCER RESEARCH?

- 1,848,923 Americans were diagnosed with cancer in 2007
- 1,289,432 Americans died of cancer in 2007
- $264 billion was spent on healthcare costs for cancer in 2006

Estimated Number of New Cancer Cases in the United States from 1998 to 2007

WHAT IS EXPENSIVE?

Is cancer research such as needed for MDS expensive?

The estimated total cumulative investment at the NCI per American over the past 30 years, including the doubling period, is about $258, or about $9 per American per year over the entire period.

"Whereas national defense spending has reached approximately $1,600 per capita, federal spending for biomedical research now amounts to about $97 per capita — a rather modest investment in "advancing the health, safety, and well-being of our people."

AAAS, ACP and other organizations recommend annual required growth rate to 5 to 6% real growth plus inflation: the annual growth rate over the past 30 years has been approximately 10%.

NATIONAL INSTITUTES OF HEALTH

FUNDING

For fiscal year 2007 there was the first true budgeted reduction in NIH support since 1970.

In 2008, for the fifth consecutive year the NIH budget failed to keep up with the rate of inflation in the cost of conducting biomedical research. Funding for NIH increased on average by 1.1% (inflation 3.7%). President vetoed Senate-proposed 3.7%

NCI: $4.8 billion, 9.6% below the 2004 funding level in real terms.

HOW DOES THIS AFFECT THE CANCER RESEARCHER?

Research requires a lot of patience

- Fate of NIH research application
  - $1,000,000 research application ($200K/year)
    - Submission
    - Review (rejection)
    - Critiques too late for next submission date
    - Resubmission
    - Review
    - Good score (acceptance)
    - Time to actual award
      - Award delayed due to continuous resolution
        - Award made including cuts
          - 15% cut recommended by study section
          - 23% mandatory across the board NCI cut
        - Total award $654,000 ($130K/year)
    - Current success rate 8%

Current success rate 8%
WHY PHYSICIAN SCIENTISTS SOMETIMES STUDY PECULIAR AND RARE CONDITIONS? WHY TO SPEND MONEY ON IT?

APLASTIC ANEMIA

Aplastic anemia is a rare disease of the bone marrow leading to destruction of stem cells, mother cells of all blood cells, resulting in failed production of all blood cells.

Paul Ehrlich described this disease and initiated research with the goal of cure.

Paul Ehrlich: Nobel Price in 1908, O'Donnall Thomas: Nobel Price 1990

Since that time AA research led to:
- Identification of bone marrow as site of blood cell production
- Concept of the “hematopoietic stem cell”
- Development of bone marrow transplantation

GENETIC CHANGES

- Inherited
- Acquired

All cells of the body affected

Polymorphism
Copy variants
Chromosomal breaks
Mutations
Epigenetic changes

DNA
Epigenetic modification
Gene
Chromosomes
Nucleus
GENOMIC/GENETIC VARIABILITY

- Epigenetic imprinting: Chemical modification of genes
- Partially reversible silencing of genes
- Mutations in cells acquired cell, not inheritable
- Inherited gene pool variability

Disease predisposition

Tiny differences within genes inherited from parents

CANCER CELL

MAJOR DEVELOPMENTS

- GENETIC AND GENOMIC TECHNOLOGIES
- NEW THERAPIES
- RETRODIFFERENTIATION OF STEM CELLS

INHERITED PREDISPOSITION VERSUS ENVIRONMENT

- Each gene may have several variants and humans inherit combination of these gene variants from parents. A combinations of millions of these variants is responsible for human diversity and differential predisposition to cancer.
GENE CHIPS AS A RESEARCH AND DIAGNOSTIC TOOL

- Gene chips
  - Ability to interrogate hundreds of thousands of gene variants to study predisposition factors for cancer, risk of complications and response to therapies
  - Screen for unlimited numbers of mutations
  - Precisely assess damage to genetic material packaged in chromosomes

Tiny pieces of silica on which hundreds of thousands of DNA probes were printed to recognize many variants of each gene when patient’s DNA is applied to them

APPLICATIONS OF GENE CHIPS

- Detection of gene variants

<table>
<thead>
<tr>
<th>Traditional methods</th>
<th>50 K Array</th>
<th>250 K Array</th>
<th>950 K Array</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 patients x 20 SNPs</td>
<td>50 patients x 50,000 SNPs</td>
<td>50 patients x 200,000 SNPs</td>
<td>50 patients x 950,000 SNPs</td>
</tr>
<tr>
<td>1000 genotypes</td>
<td>2,500,000</td>
<td>12,500,000</td>
<td>47,500,000</td>
</tr>
</tbody>
</table>

3 months of work for 1 PhD

1 week of work for 1 PhD

Example cytidine deaminase gene variants

Gene variants
- AC=best outcome
- AA=decreased sensitivity, early relapse
- CC=increased sensitivity, high toxicity

Modification of therapy based on gene variant present

APPLICATIONS OF GENE CHIPS

- Identification of chromosomal defects

RESULTS IN LEUKEMIA

Routine test vs Gene array:
- Normal
- Abnormal
CHALLENGES

- Expense: expensive technology but cost is coming down
- Expertise: very unique combination of skills needed:
  - cancer biologist/researcher/populational geneticist/statistician
- Difficult to catch up with technology:
  - 10K, 50K, 250K and 950K chips,
- Informatic needs:
  - Array experiments generate 20 Gb per day
  - Framingham database of controls: 2 Tb 2000Gb. This database has 6000 250K gene chips in 5 modules: it takes 18h to download one module. Of note is that Cancer Center network is 2Tb

GENE CHIP AS A FUTURE DIAGNOSTIC TOOL

- Can be performed at birth
- Could contain all important genetic risk factors
- Does not have to be repeated
- Can become a property of the patients
- Could be used for prevention or in the case of illness to aid diagnosis
- Chip can contain 6000 important diagnostic gene variants
  - Cancer risk
  - Drug toxicity/sensitivity
  - Complications, thrombotic risk
  - Immune responsiveness

NEW THERAPIES
PARADIGM FOR NEW THERAPIES-
MOLECULAR TARGETING

Healthy cells → Transformation → Cancer cell

Mutations → Defective protein → Gene

Find chemicals which can reverse the defect → Develop new drug

MOLECULAR TARGETED THERAPIES

• Example:
  Chronic myeloid leukemia (CML)- a deadly blood cancer
    – Discovery of a broken chromosome 'Philadelphia chromosome'
    – Discovery of a fused gene bcr/abl and its function
    – Study of chemicals which block the mutant gene
    – Clinical trials of Gleevec in patients
    – Introduction of Gleevec, new drug that induces remission in 90% of patients with CML

TARGETED AGENTS VS. OLD CHEMOTHERAPY

• Traditional chemotherapy kills malignant cells such as present in MDS.
  – Tumor kill depends on the dose
  – Toxicity to normal cells – balance
  – Resistance
• Targeted therapies aim at specific defects present in the tumor cells
  – No need for dose escalation –
  – Normal cells likely resistant
  – Response rate higher if patients with specific target defects can be identified
FINDING NEW MUTATIONS

• New mutations constitute specific targets for selective drugs to minimize toxicity and maximize effects
• Specific mutations can point towards use of selective drugs and maximize response in selected patients.

CHROMOSOMAL BREAKS

UNIPARENTAL DISOMY

DELETION

Hemizygosity for Germ line mutation

Hemizygosity for Germ line mutation/ SNP

Inactivation inherited somatic mutation

TET2

106,287,392-106,420,407

PPA2

106,612,474-106,614,625

4q24

Chromosome 4

CMML-1 + CLL

CMML-1 to sAML

CMML-1

CMML-2 to sAML

RARS*

RAEB-2*

CMML-2  to sAML

CMML-1

RCMD-RS

MDS/MPN to sAML

RCMD*

RCMD-RS

RCMD-RS (MC)

New gene mutations

• Jak2
• C-Cbl
• Ras
• TET2

Found in MDS at CCF
TARGETING NEW MUTATIONS

- **JAK2 mutation**
  - A mutation that permanently activates JAK2 protein in the stem cells to stimulate cell divisions
  - Present in patients with myeloproliferative syndromes but also sometimes in those with MDS/MPD and MDS
  - Detection tests are available
  - New Jak2 inhibitors in testing

- **C-Cbl mutation present in 5-10% of MDS**
  - Drugs in development

- **TET2 mutations present in 20% of MDS**
  - Possible treatment by hypomethylating agents

EPIGENETICS

- Chemical modification of DNA fragments to turn on or block specific genes
- Unlike mutations – epigenetic changes can be reversed
- Normally, responsible for generation of specific tissues during human development

- In cancer cells, epigenetic DNA modification is aberrant: many tumor suppressor genes are epigenetically blocked.
- Epigenetic therapies reactivate tumor suppressor genes.

EPIGENETIC THERAPIES

- Vidaza and Dacogen are hypomethylating agents and constitute examples of epigenetic drugs
- Current response rates 20%
- Search for marker of response to identify patients who will respond and spare those who will not from potential toxicities
- Development of oral forms of these drugs
- Development of low-dose therapies to improve response and decrease toxicity
NEW GROWTH FACTORS

Hormons which work on the specific marrow cells to produce more of specific blood cells

- Procrit/Epogen, Aranesp to boost red cells
- Neupogen/Neulasta to boost neutrophils
- Eithrombopag/Nplate to boost platelets

All already available but not all FDA approved for MDS

NEW IMMUNOSUPPRESSIVE DRUGS

- In some patients immune system attacks bone marrow stem cells and block blood cell production
- Old drugs ATG and CsA— not elective and toxic
- New targeted drugs with minimal side effects
  - Zenapax, Abatacept, Amevive

Thank you
ADULT STEM CELL RETRO-DIFFERENTIATION

- All cells in the body have a silenced potential to produce all tissues, this potential is encoded in the DNA which is identical in all cells.

- Multipotent stem cells have a potential to produce all tissues, similar to the ultimate stem cell: the fertilized egg.

- Through a process of differentiation, tissues and organs are formed and assume specific function and shape

Why it would not be possible to isolate cells and revert them into a multipotent stem cell and direct their program to regenerate diseased tissues?

POTENTIAL OF THE ADULT STEM CELLS

Skin cells

Transfer of 4 genes

Marker gene

Important for stem cells

So that they are turned on

Retrodifferentiation

Multipotent stem cell

Transfer into 8-cell embryo

Mouse with green organs

THERAPEUTIC POTENTIAL OF THE ADULT STEM CELLS

Allogeneic bone marrow transplant is limited by the availability of the donor, toxicity of GvHD and inability to replace diseased bone marrow stem cells

Retrodifferentiation

Adult embryonic stem cells

Expansion

Differentiation into bone marrow stem cells

Therapy of leukemia

Aplastic anemia

Transplant to replace

Damaged stem cells