Science on the NIH Road Map: The Center for Nutrient-Gene Interaction (CNGI) in Cancer Prevention

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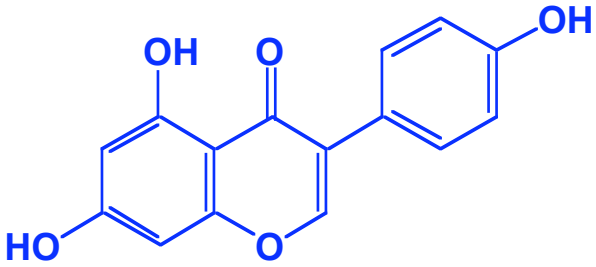
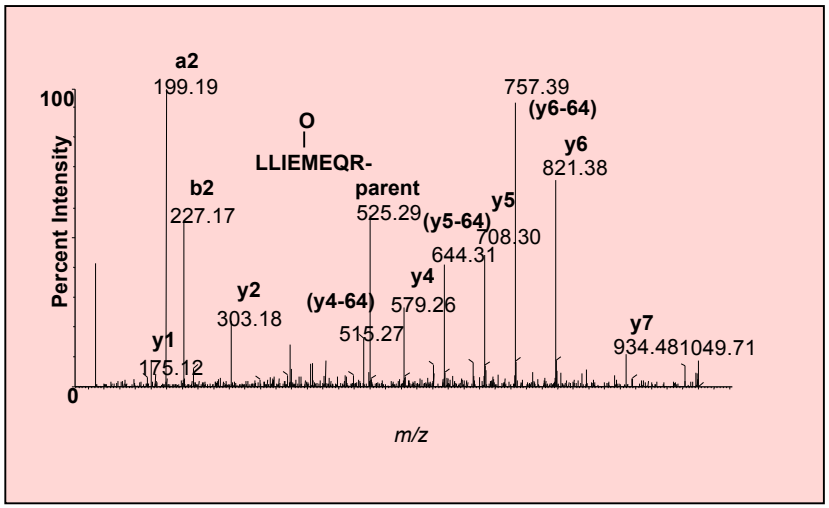
CNGI Seminar 11-19-03

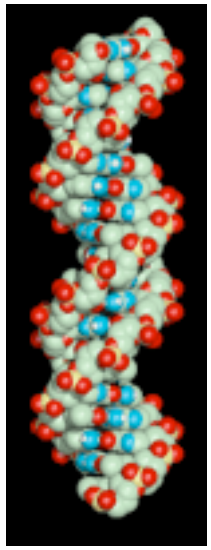


genistein

UAB
Northern California Cancer Center
U. Penn
U. Missouri-Rolla

A multi-disciplinary multi-institutional center





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Synopsis of this talk

- NIH and its beginnings - development of the research paradigm
- Cancer research - the search for the cure
- Living with estrogens (and polyphenols)
- Cancer Research - the shift to prevention - a role for CNGI
- How is the NIH research paradigm changing?

Origins of NIH research

Marine Hospital, c.1887

Hygiene Lab, DC -1891

Artist's 1948 sketch for the NIH Clinical Center. NIH Historical Office photographic archive.

Bethesda -1948

1930 - Ransdell Act establishes the National Institute of Health

1937 - National Cancer Institute established

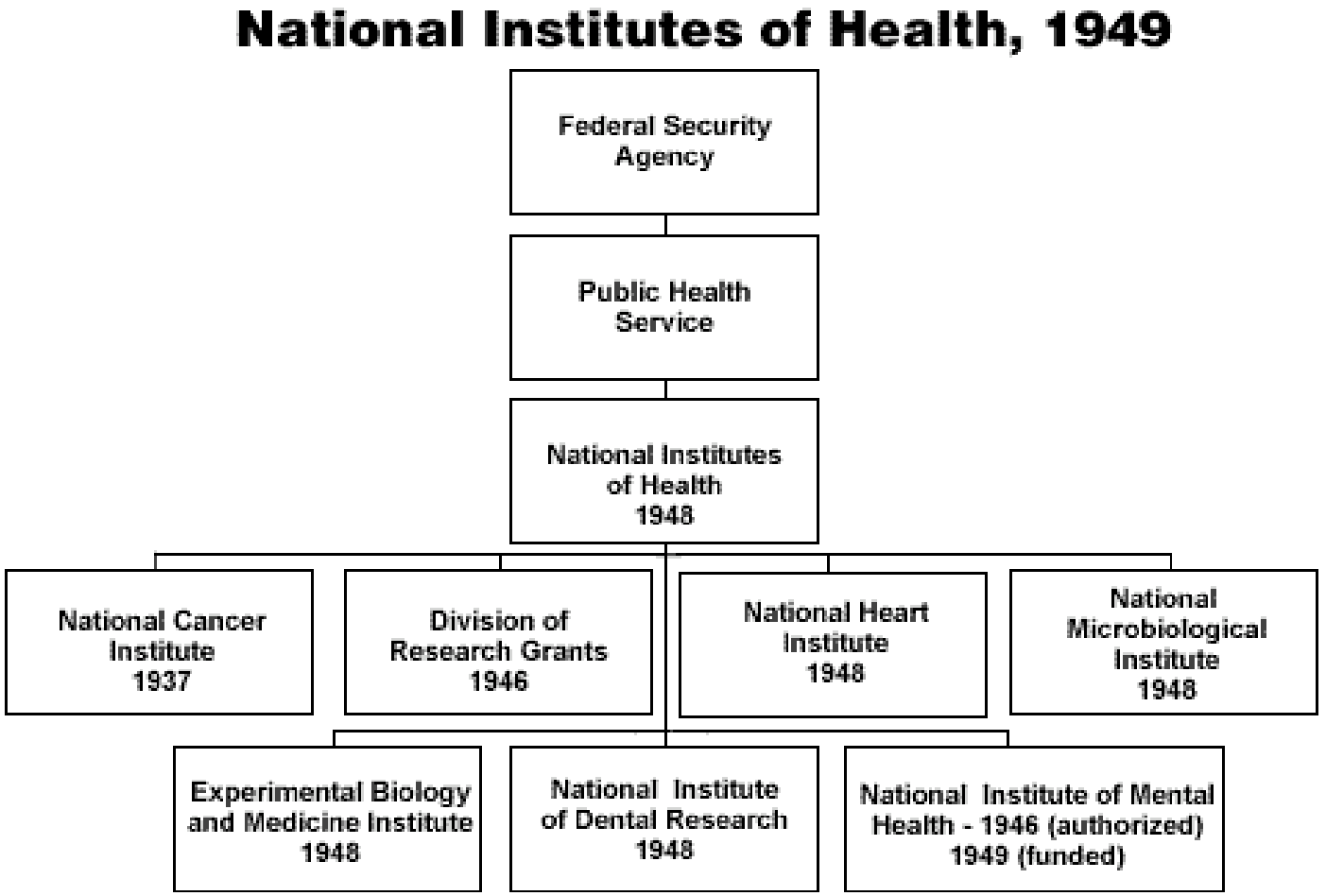
1948 - Four new institutes (cardiac disease, dental disorders, infectious diseases, and experimental biology and medicine) and a Clinical Research Center leads to the *National Institutes of Health*

1971 - National Cancer Act

1990 - Human Genome project

1998 - Twenty seven institutes and centers constitute the National Institutes of Health

Origins of Federal Biomedical Research



NIH funding

1937 National Cancer Institute starts grants and fellowship program

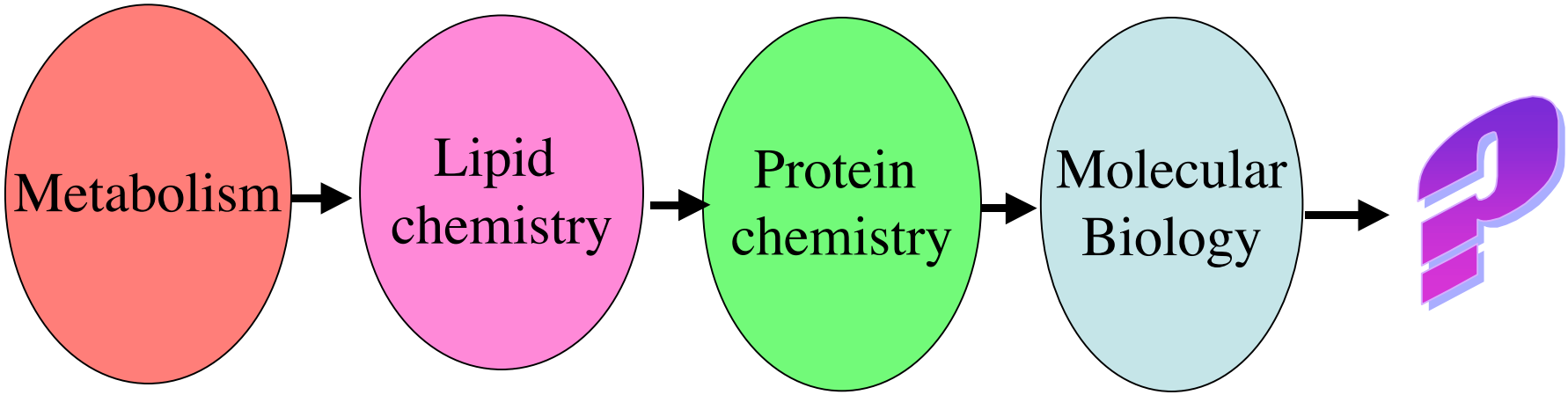
1946 Extended to NIH

- 1947 $4 million
- 1957 $100 million
- 1966 $1 billion
- 1990 $8.5 billion
- 2002 $23.3 billion

NIH research is linear

- Universities have been increasingly dependent on their development on NIH funding since 1980 (Nature)
- Has been determined by Study Sections
  - Approve what they in their narrow view consider the "best science"
  - Most data and least controversy wins
  - Until 2003, organized according to major scientific divisions
  - In 2003, reorganized around organ systems

Direction of NIH research for the past 50 years



Cancer Research - the search for therapy

- The immense amount of research funding over the past 60-70 years has been focused on treating the patient who has presented with cancer
- There have been successes - some cancers have been substantially reduced
- Stomach cancer is down 90% since the 1930's, but it was due a preventive policy

Origins of CNGI at UAB

- 1985 Recruitment of Clint Grubbs
- 1986 Recruitment of Coral Lamartiniere
- 1987 American Cancer Society fund first soy and breast cancer prevention grant (SB/CG)
- 1988 American Institute for Cancer Research continue soy funding (SB/CG)
- 1994 NCI fund an integrated research program grant (IRPG) on genistein and breast cancer (SB/CAL/HW)
- 1997 NCI renew IRPG (SB/CAL)
- 1999-2003 Many USAMRD and NIEHS prevention grants to CAL
- 2000 Botanicals Center for Age-related Disease
- 2003 NCI fund CNGI in cancer prevention

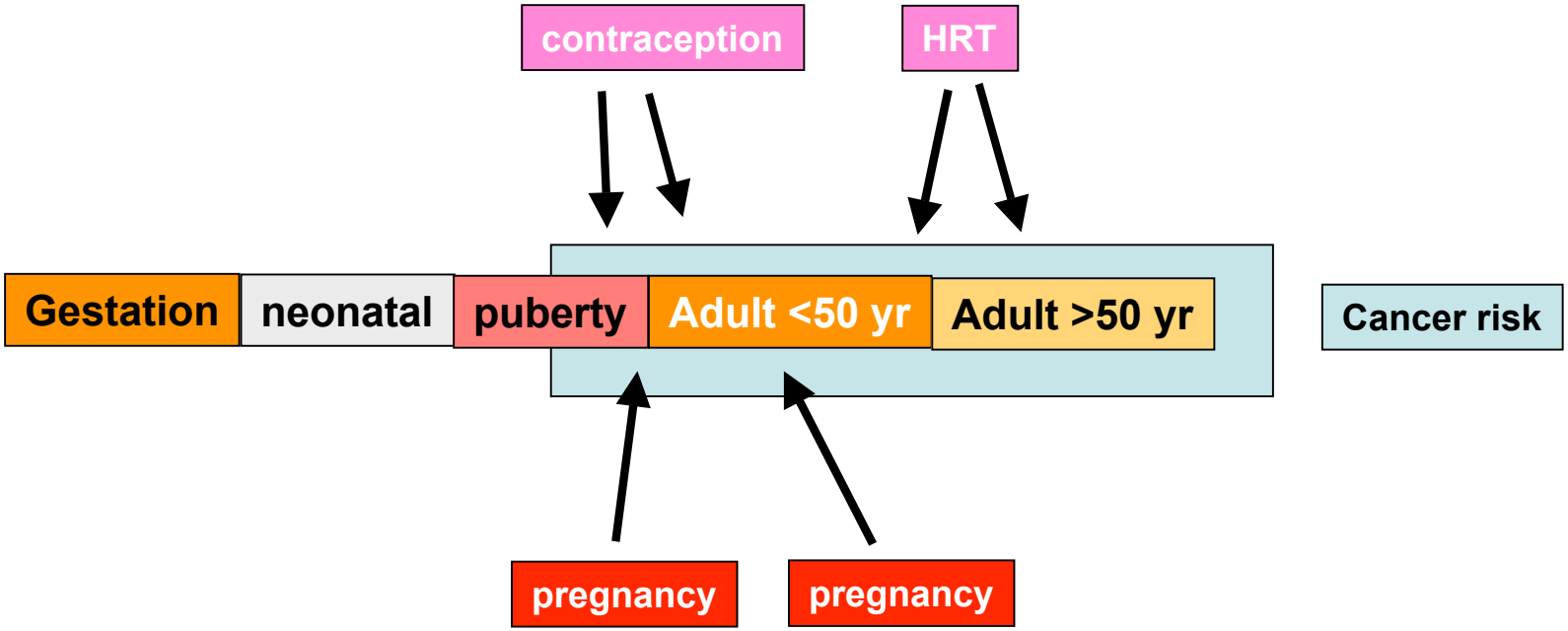
Can cancer be prevented?

- Public health policy has had success in lowering the incidence and death from of stomach cancer
- Control of smoking in public places may also reduce the lung cancer rates
- What are the events that increase cancer?
  - Environmental chemicals in air, water and food
  - Endogenous compounds that are altered by social habits

Estrogens
do they define you, me and cancer?

- **We are exposed to high estrogen levels during gestation, during puberty, and during the early part of adult life**
- **Toxicologists are passionate about defining so-called *endocrine disruptors***
  - **compounds that appear in the environment that have steroid-like activity (contraceptives and other therapeutics that are flushed down the toilet)**
  - **estrogenic chemicals produced by the chemical industry**
  - **estrogens in foods**

Timeline for estrogen exposure and breast cancer



Effects of estrogen on breast cancer risk at different ages

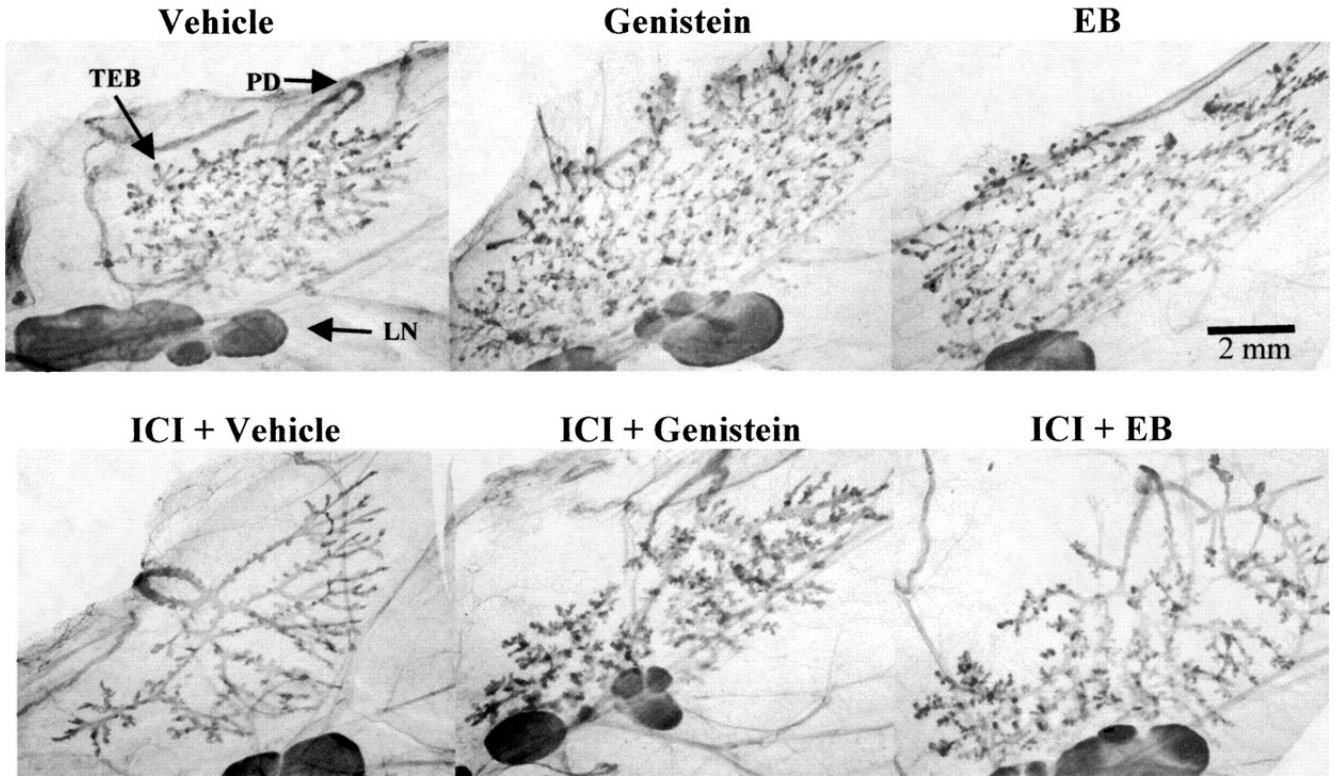
- Gestational - genistein allegedly pro-cancer
- Neonatal - DES and genistein prevent cancer
- Pre-pubertal - estradiol/progesterone strong prevention, genistein weaker
- Pregnancy - mixed (increased early, less in later years)
- Contraceptive - mixed
- HRT - 2% increased risk per year of use

Summary: estrogens have complex effects

Puberty is a crucial period for estrogen exposure

- The early part of puberty is associated with mammary epithelial cell proliferation
  - See work of Russos' and Lamartiniere groups
- This is followed by differentiation of the terminal endbuds
- Differentiation limits the number of cells containing damage to DNA
- Estrogen exposure at this stage may also control estrogen responsiveness in adult life
- Are related compounds capable of altering responsiveness?

Genistein is an estrogen in the rat mammary



Cotroneo et al., Carcinogenesis 23:1467, 2002

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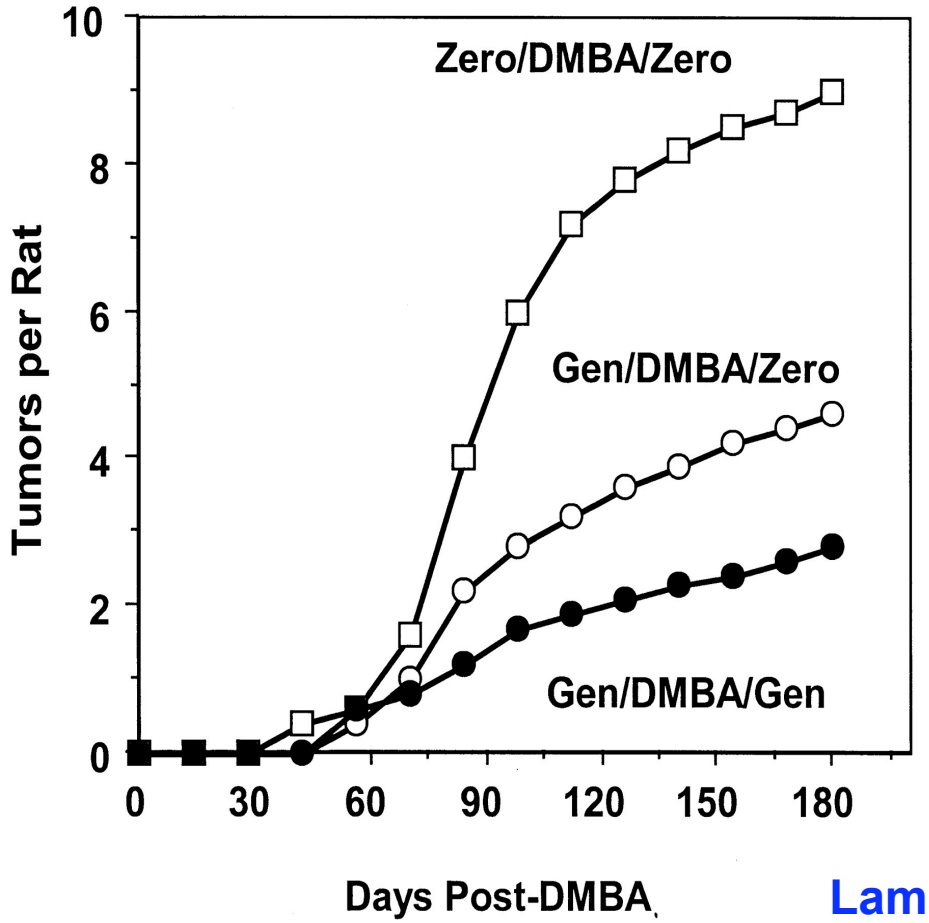
Early genistein exposure is essential for cancer prevention



Dietary genistein in adult life is only effective if the animals were given genistein during the prepubertal period

Lamartinere et al., J Nutr 132:552S

Epidemiologic evidence in support of pubertal prevention in Asia-Americans

Adolescent	Adult	Risk
Low	Low	1.00
Low	High	0.93 (0.58-1.48)
High	Low	0.77 (0.51-1.16)
High	High	0.53 (0.36-0.78)
P trend		0.001

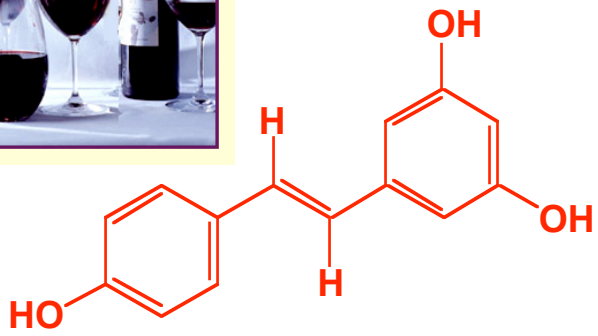
Wu et al., Carcinogenesis 23:1491 (2002)

Soy in adolescence and Shanghai breast cancer study

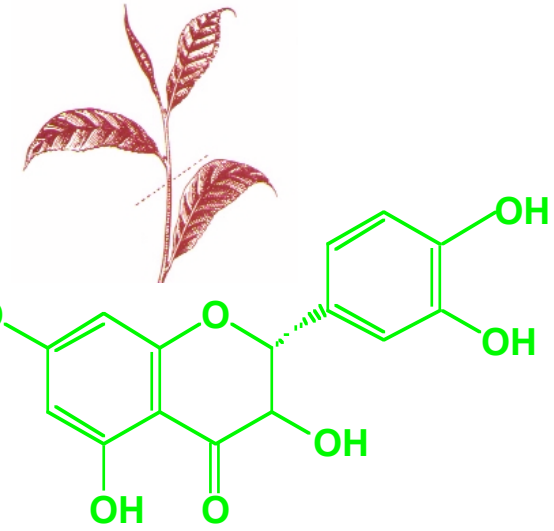
Food	Q1	Q2	Q3	Q4	Q5	p trend
Premenopausal						
Tofu	1.00	0.72	0.87	0.60	0.79	<0.02
Not tofu	1.00	0.90	0.76	0.68		0.01
Postmenopausal						
Tofu	1.00	1.10	0.89	0.82	0.62	0.01
Not tofu 1.00	0.77	0.93	0.62		0.05	
Reports from mothers						
Tofu	1.00	1.08	0.72	0.52	0.65	<0.01
Not tofu 1.00	1.10	0.72	0.79	0.44	<0.01	
Fresh legumes	1.00	0.77	0.92	0.83	0.96	0.82

Shu et al., Cancer Epidem. Biomark. Prevent. 10:483, 2001

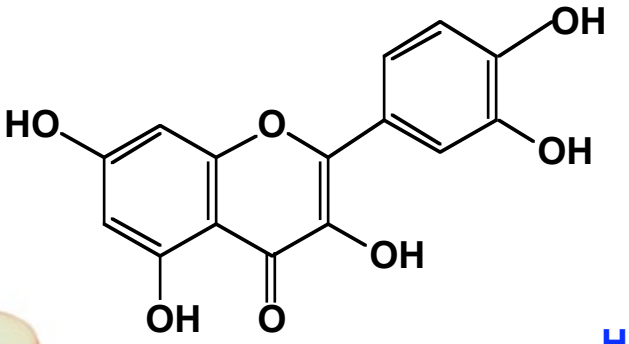
Polyphenols and disease risk



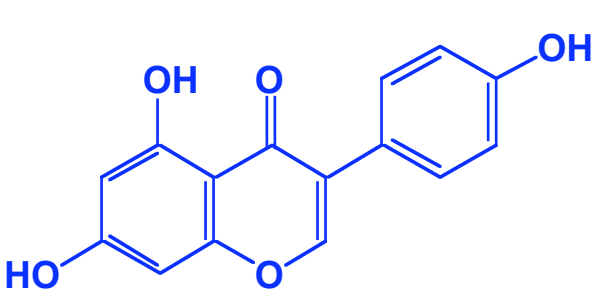
resveratrol



catechin



quercetin



genistein

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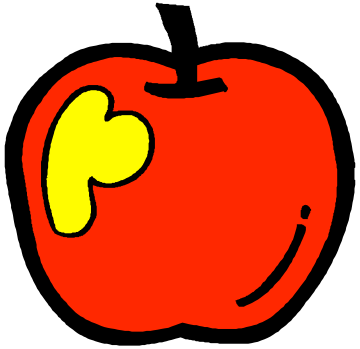
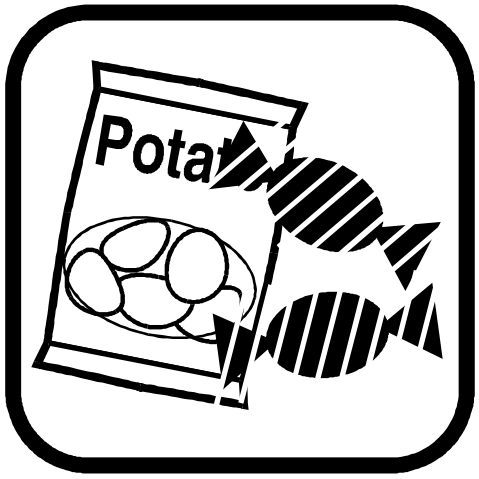
Eating habits at age 12





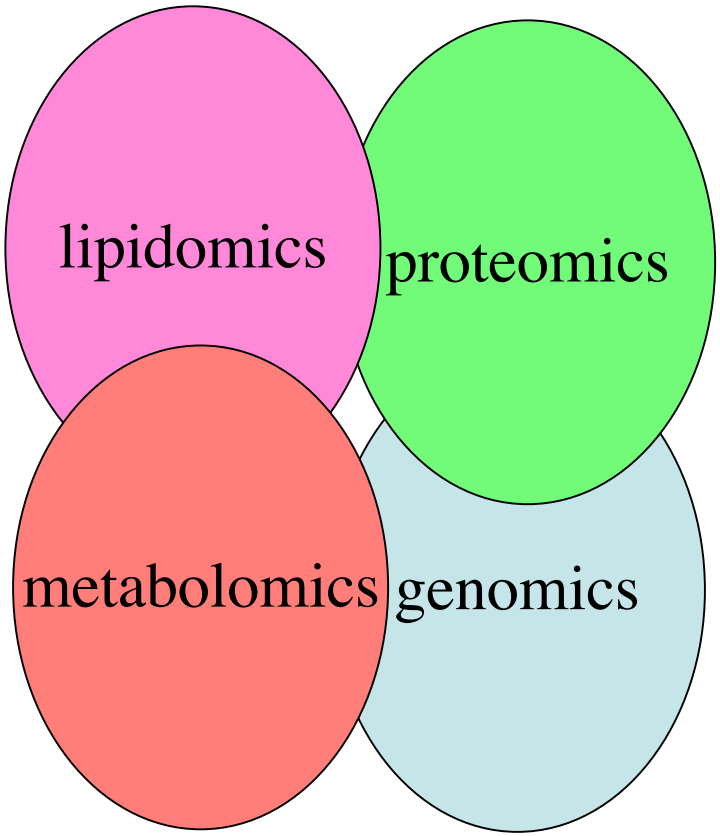
What are the real activities of genistein and other polyphenols?

- Could be estrogens
- What else?
  - Tyrosine kinase inhibitors
  - Numerous other activities
  - DING protein - a possible analog of Dvl in the Wnt signaling pathway
- Future may lie in the use of DNA microarrays

Evolution of the change in linear research

- A substrate to search for one enzyme activity
- A labeled oligonucleotide or cDNA to probe a library
- Combinatorial chemical library with enzyme or receptor
- An agonist or antagonist to probe a gene array to locate genome-wide or pathway-wide targets
- Mixture of agonists or antagonists with gene arrays
- Protein arrays to find protein-protein interactions

The future of NIH research

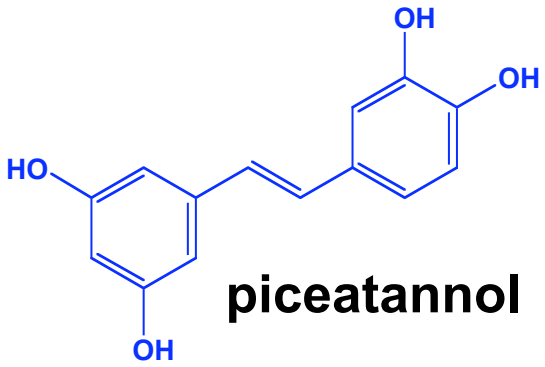


Integration for life extension in yeasts

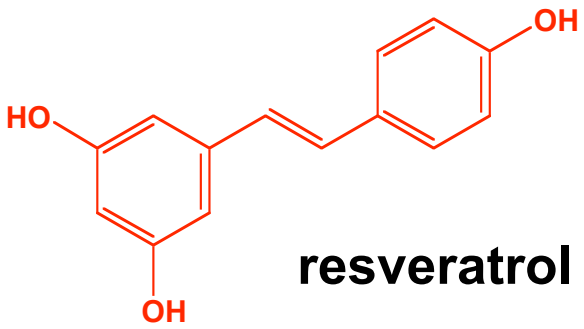
Caloric restriction increases yeast life span - dependent on the SIR-2 gene (a sirtuin) - a NAD^+-dependent deacetylase - calorie restriction increases NAD^+

Human equivalent SIRT1 - deacetylates p53 (used K382 peptide)

Sinclair et al. screened a library of compounds - quercetin and piceatannol emerged as activators of deacetylase



piceatannol



resveratrol

Resveratrol increased life span of the yeast by 70% in the absence of caloric restriction, decreased p53 K382 acetylation, and reduced the frequency of repetitive DNA recombination

Technologies favored by the NIH roadmap

- Molecular Libraries and Molecular Imaging
- Bioinformatics and Computational Biology
- Nanomedicine
- Structural Biology
- Building Blocks and Pathways
  - Gene arrays
  - Proteomics
  - Metabolomics/metabonomics

Protein analysis 2003

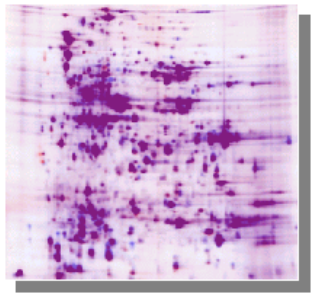
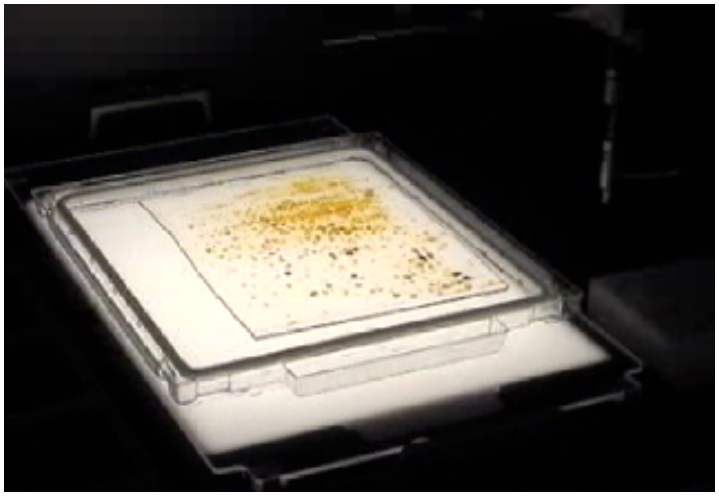
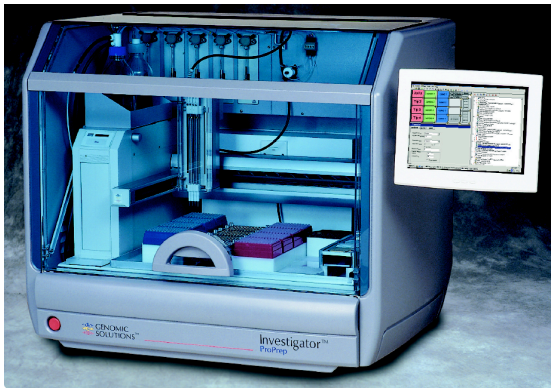


Image analysis

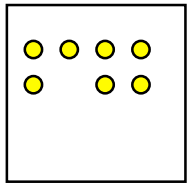
Robotic spot picking



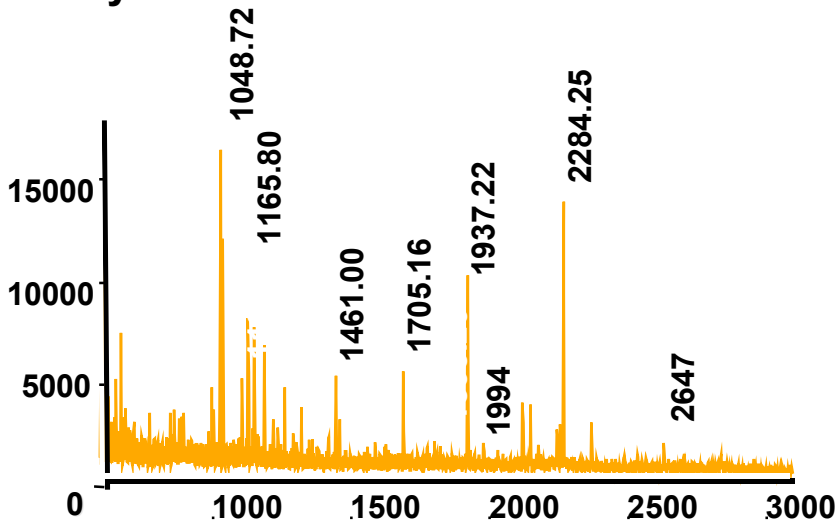


Destaining. drying and trypsinolysis

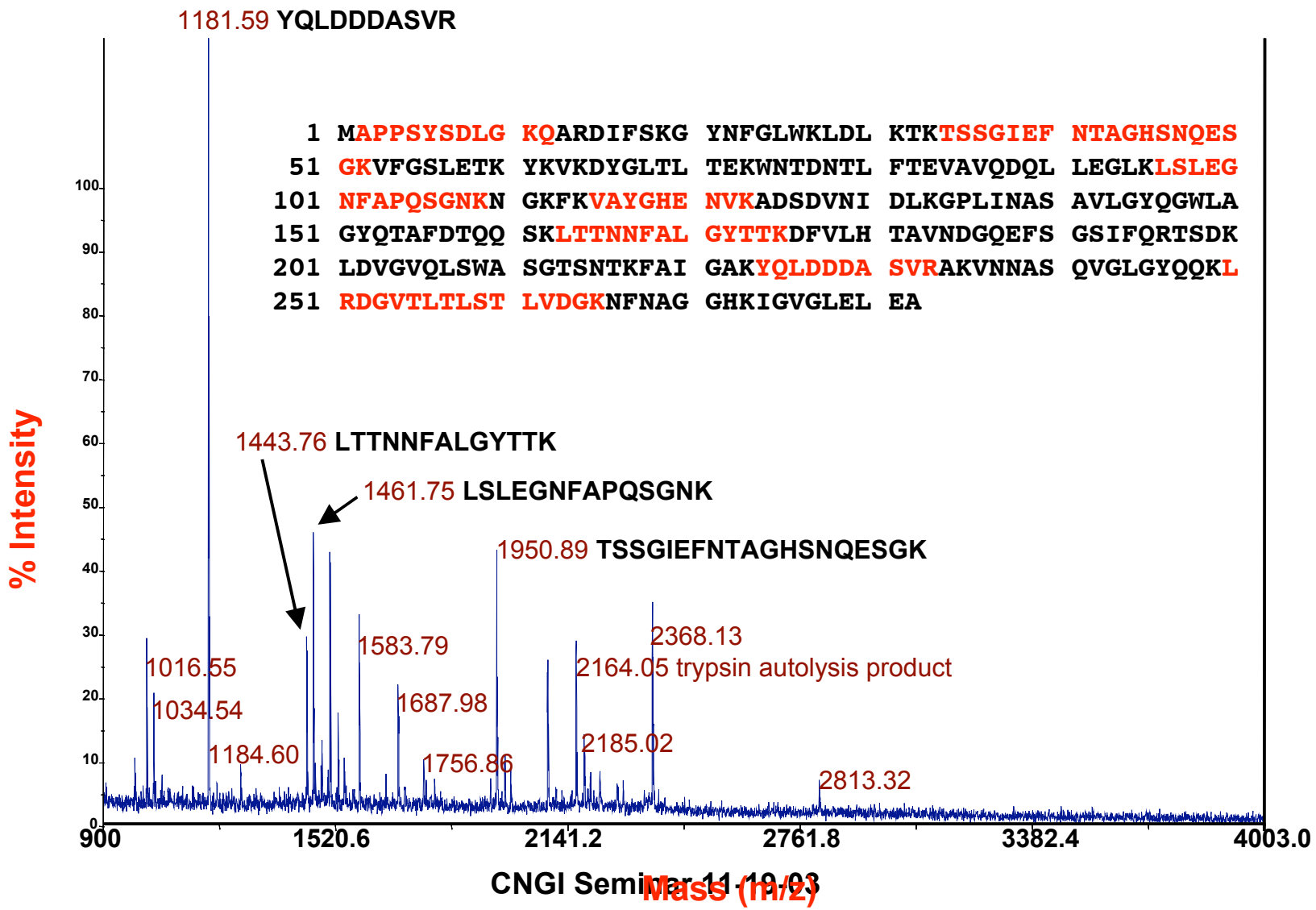
MALDI plate



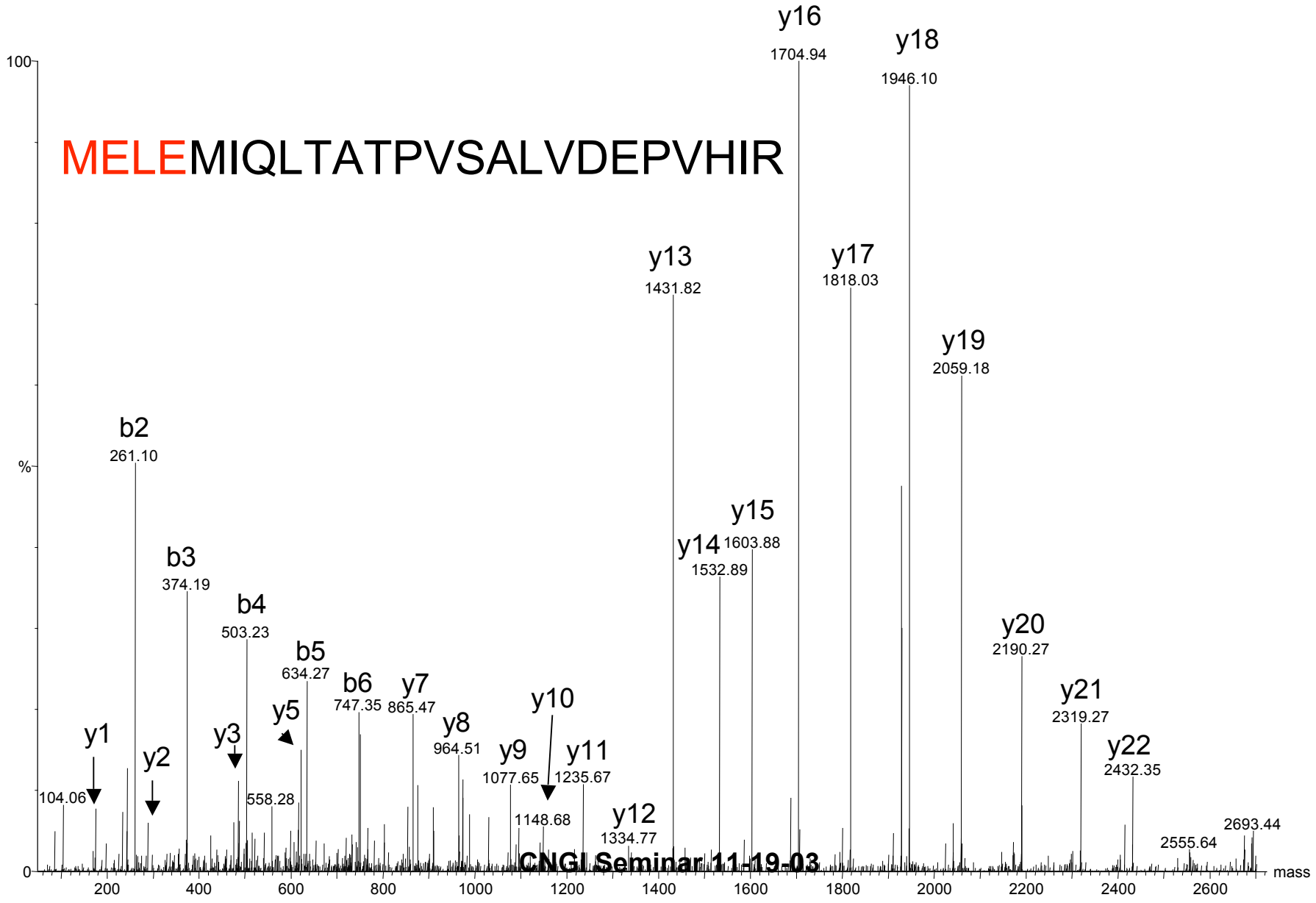
Desalting Ziptip



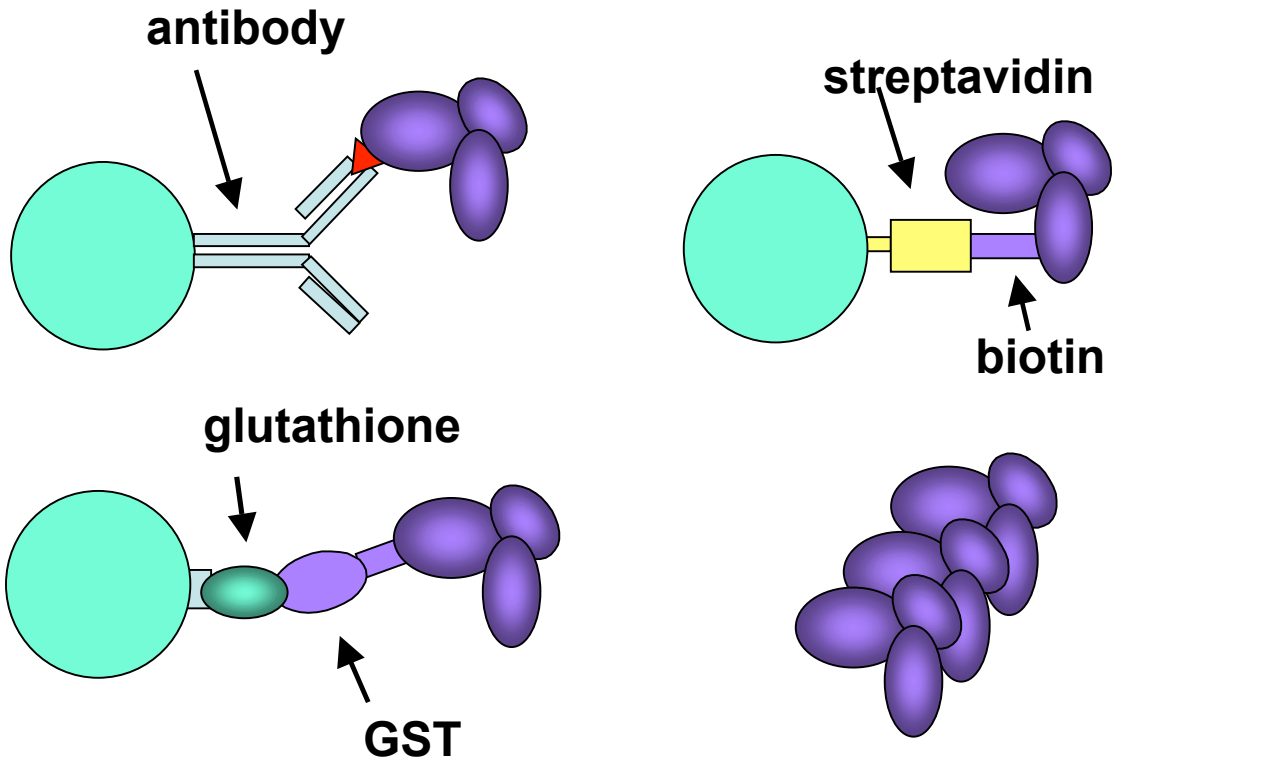
Tryptic mass fingerprint of a porin from *Drosophila*



Unexpected peptide from a bacterially expressed protein



Understanding the protein-protein network



Mapping the protein:protein network by antibody or affinity isolation

Summary

- The NIH Roadmap represents a challenge to the science community
  - It's time to cure disease
- The roadmap is supported by all the NIH institutes
- It requires the integration of widely separated skills, particularly in high level computing, statistics and nanotechnology

2003 CNGI Pilot Program

Deadline:	**December 9th, 2003**
Format:	**NIH 398 with a 10-page restriction for sections A-D**
Deliver to:	**454 McCallum or by e-mail to Rose.Johnson@ccc.uab.edu**
Topic:	**Dietary polyphenols, a cell or multi-cellular organism model that responds to steroids, pathway exploration**
Other:	**Use of genomics, proteomics, and/or statistics cores**
Award:	**$25,000-$40,000 (3-5 awards)**

Principal hypotheses in UAB CNGI

- That the set points of expression of genes that are under the control of steroid hormones during puberty are strongly associated with adult cancer risk (Lamartiniere)
- That the set points are controlled both by the polymorphisms of the genes and by dietary polyphenols (Horn-Ross, NCCC)
- And that extracting the answers from high dimensional data requires the discovery and implementation of novel statistical and computing techniques (Allison)

Core Support in UAB CNGI

- Administration (Barnes/Grubbs)
- DNA analysis: DNA microarrays and gene polymorphisms (Guay-Woodford)
- Proteomics and mass spectrometry (Kim/Barnes)
- Biostatistics and Bioinformatics (Soong/Chen/Desmond/Hill/Lefkowitz/Meleth/Page)

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