GSB/FBDD

LRL-CAT: A company's experience at the APS

Stephen R. Wasserman

Answers That Matter.

References to Industry

- On front web page of light source
- United States
  - NSLS: no
  - ALS: no
  - SSRL: no
  - APS: in research highlight only
- Other Countries
  - CLS: yes
  - Diamond: yes
  - ESRF: yes
  - Spring8: End of run report
  - ANKA: yes (hard to see)
  - DESY: no
  - SSRF: yes

Australian Synchrotron: no

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Outline

- History
- Use of beamline
- Philosophy of operations
- Finance
- Thoughts on industry

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History

- Structural GenomiX
  - Incorporated in 1998
- SGX Pharmaceuticals
  - Name change 2005
- Eii Lilly and Company
  - Purchased 2008

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Why the APS?

- Decision to use APS made in 1997
  - 3rd generation source
  - Insertion devices
  - Alternatives had lower flux
    - NSLS, SSRL, CHESS – 1st and 2nd generation
    - ALS – soft x-ray energy range
  - SGX personnel had connections to APS
  - Lab and office accommodations
  - Beamline could be “wholly owned”

PROPOSAL
for a
COLLABORATIVE ACCESS TEAM
for
STRUCTURAL GENOMICS
at the
ADVANCED PHOTON SOURCE

K.L. D’Amico
X-ray Analytics, Ltd.
and
W.A. Hendrickson
Columbia University
May 1997

Abstract
This proposal describes a synchrotron facility designed to support the rapid and accurate determination of X-ray crystal structures for large numbers of biological macromolecules. The subjects for study are gene products chosen in relation to whole genome sequences with the ultimate aim to provide structural paradigms representing all major protein families from all forms of life. The proposed facility comprises one sector of the Advanced Photon Source to be equipped with a Bending Magnet beamline and two undulator stations that will operate simultaneously from independently tunable tandem undulators. Funding for the facility will be committed in full by commercial sponsors.

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"Our drug discovery efforts are dependent on continued access to and use of our beamline facility…"

Prospectus, Initial Public Offering

SGX Pharmaceuticals, Inc.

January 31, 2006

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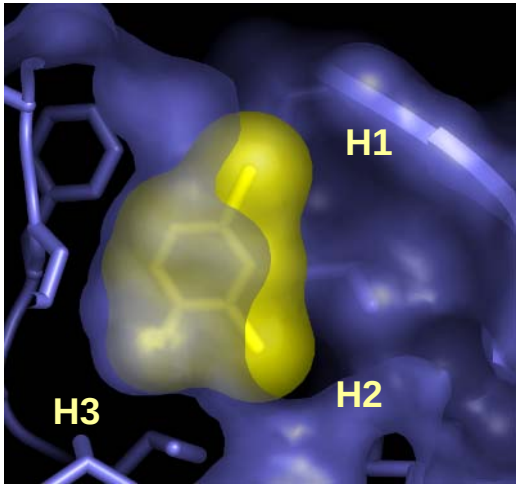
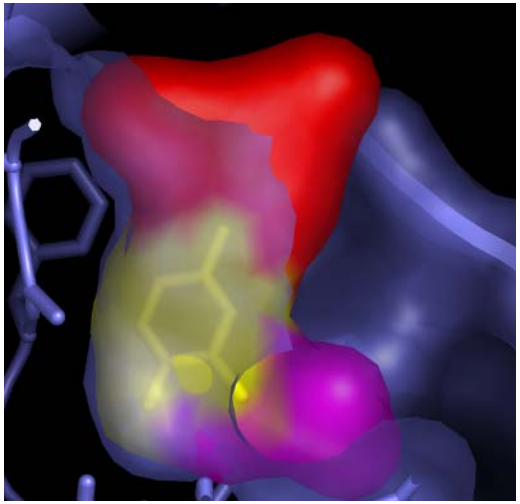
Fragment Hit to Lead Process





- ***FAST* Scaffold library screen**
- **Literature precedents**
- **Structure-guided triage process**
- **Pick "promising" opportunities**
- **Explore SAR**

- **Opportunities from Structure**
  - Confirm binding mode
  - Interrogate scaffold
    - make ring/break ring, atom "walks"
    - conformational hypotheses
    - target-inhibitor knowledge
    - lead merging (*SMERGE*)
    - end game

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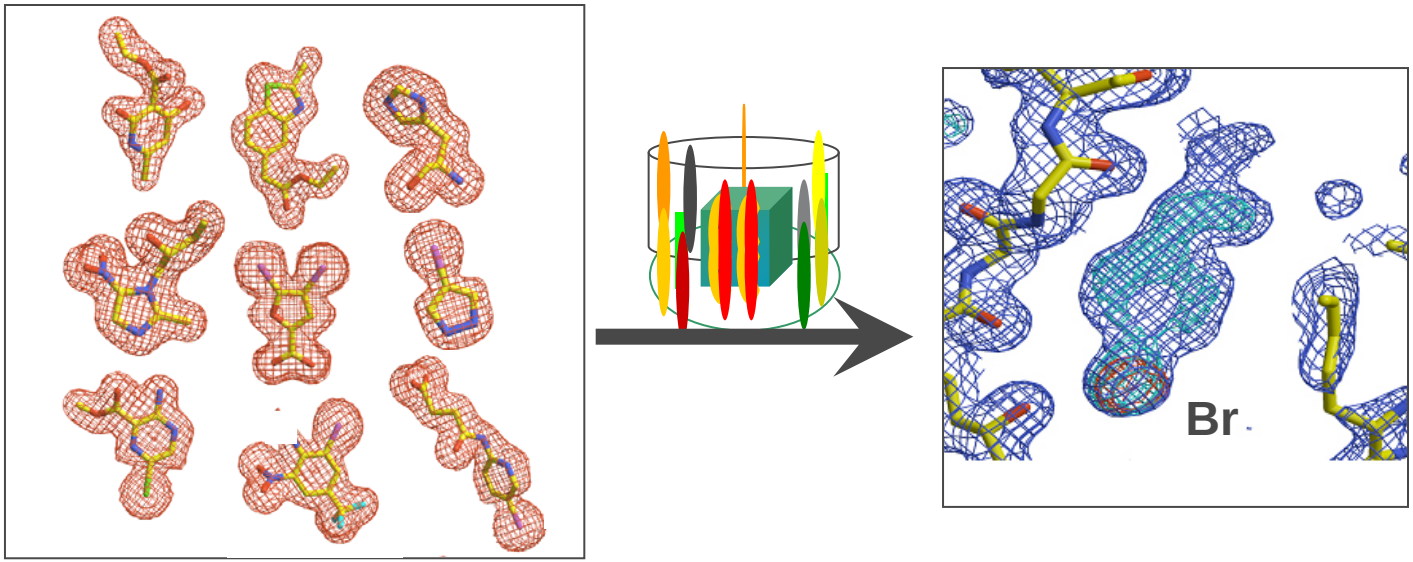
Crystallographic *FAST*™ Scaffold Screening



- Fragment library is divided into 150 pools of 10 shape diverse compounds
- Pools are soaked into pre-formed crystals
- Br atoms serve dual roles
  - synthetic handle
  - sentinel in electron density map
- Identify scaffold
  - shape of electron density map
  - anomalous bromine signal
- Hit rate: 1 – 5 %

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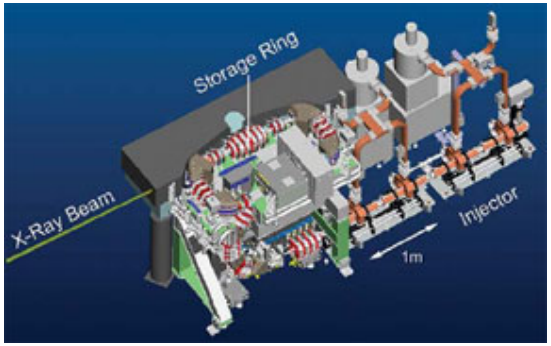
Beamline as a Home Source



- X-ray Home Sources
  - Rotating Anode
  - Compact Light Sources
    - Tunable
    - Potentially equivalent to 2nd generation synchrotron
- Synchrotron beamline as a home source
  - “Walk-in” access
  - No advance scheduling
- Goal of automation to provide equivalent sample turnaround

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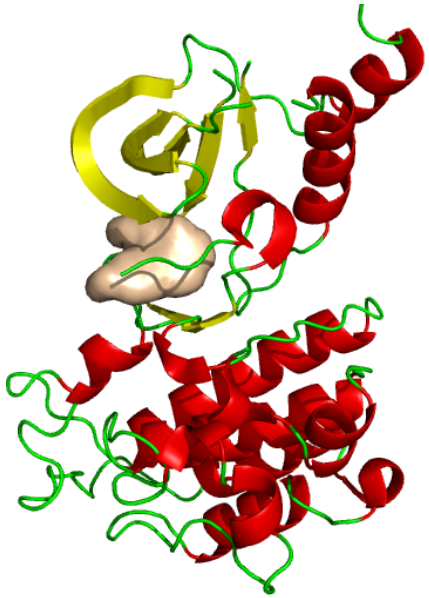
Philosophy of SGX-CAT

- Integrate directly into structure solution and drug discovery processes
- Robust
- Rapid upgrades and maintenance
- Automated
- Control processes
  - At beamline
  - Crystallization



- Evolution from data collection to data management
- SGX-CAT aims to be virtually user-free

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Automated Processes

- Crystal loading
- LN_2 to remove surface ice
- Loop centering*
- Crystal screening
- Crystal quality score and resolution estimate*
  - Selection of best crystal within group of duplicates*
- Beam attenuation*
- Data collection
- Data processing*
- Quality control*
  - *Use automated decisions

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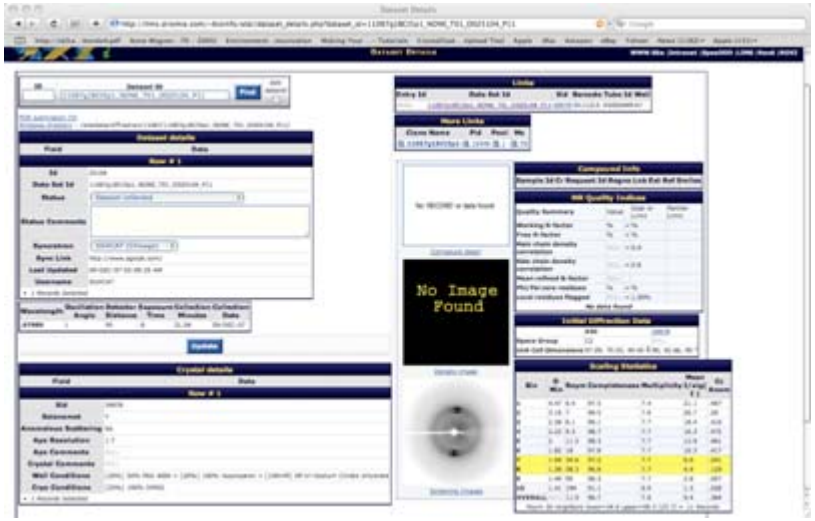
Integration into Drug Discovery

- All sample information and results stored in Oracle database
- Description of crystals provided electronically
  - Direct entry into database (Lilly/PSI2)

  or
  - Spreadsheet (Partners/General Users)
- Two direct T3 connection between LRL-CAT and Lilly-San Diego and Lilly-Indianapolis
- Database used simultaneously at the beamline and Lilly San Diego and Indianapolis locations
- Rapid access to results
  - Screens: 4 minutes
  - Datasets: 20 to 180 minutes



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Costs: Home Source

- State of the art system (rotating anode): $817,000
- Installation: $40,000
- Annual depreciation (5 years): $172,000

- Annual service contract: $60,000
- Operation: 1.0 FTE, $250,000

- Available hours (year round, 90% efficiency): 7884

- Cost per hour: $61

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Costs: APS Protein Beamline

- Build: ~$10,000,0000
- Annual depreciation (10 years): ~$1,000,000
- Annual operating budget: ~$1,000,000
- Available Hours: 3375 (3750 at 90% efficiency)
- Operating cost per hour: $593
- Proprietary charge: $375
- Cost per hour: $968 ($671 without depreciation)

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Cost per datum

- Dataset:
  - Home source
    - 1 to 6 hours
    - $61 to $366
  - LRL-CAT
    - May 27, 2009
    - 13.2 minutes (0.22 hours)
    - $212
    - October 1, 2010
    - 9 minutes (.15 hours)
    - $145
  - State of the art detector
    - $83

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Cost per datum

- Screening
  - Home source
    - ~6 minutes
    - $6 per crystal
  - LRL-CAT
    - Today
    - ~4.5 minutes
    - $72 per crystal
    - October 1, 2010
    - ~2 minutes
    - $32 per crystal
- Robotics are limitation

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Financial conclusion

- 3rd generation synchrotron beamline is cost effective IF EFFICIENT

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Why use the APS?

- Upstream
  - Smaller crystals compared to laboratory source
  - Savings in crystallization time
- At APS
  - Intense source
  - Tunable – anomalous experiments
  - High data rate
    - Opportunity cost of research
- Downstream
  - Data quality
  - Automatic data analysis

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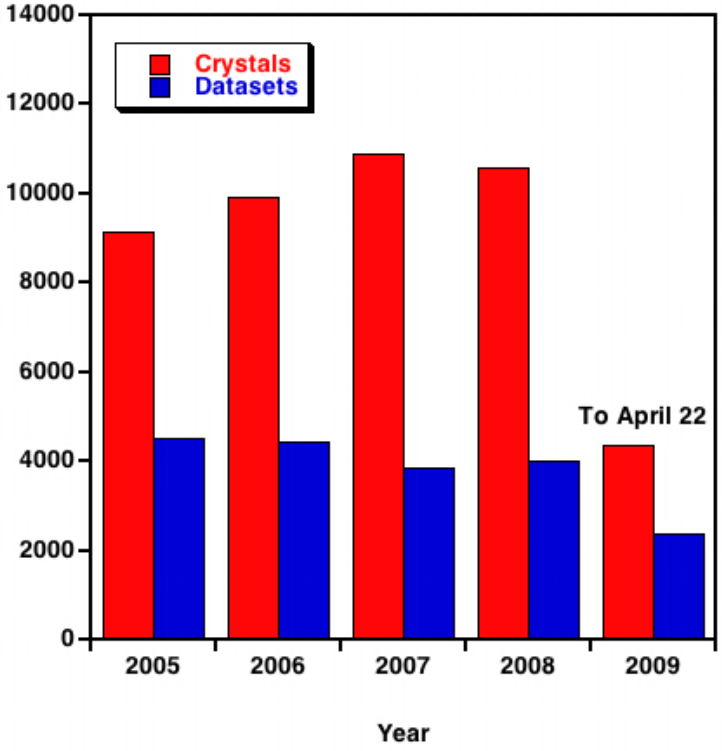
Statistics



- 2008
  - 10,594 crystals
  - 4022 datasets
- 2009 Run 1
  - ~25% more crystals
  - ~70% more datasets

- >80% of datasets scale and reach desired resolution limit
- Resolution for internal crystals (2008)
  - Median: 2.1 Å
  - Mean: 2.2Å, Std. Dev. 0.8 Å

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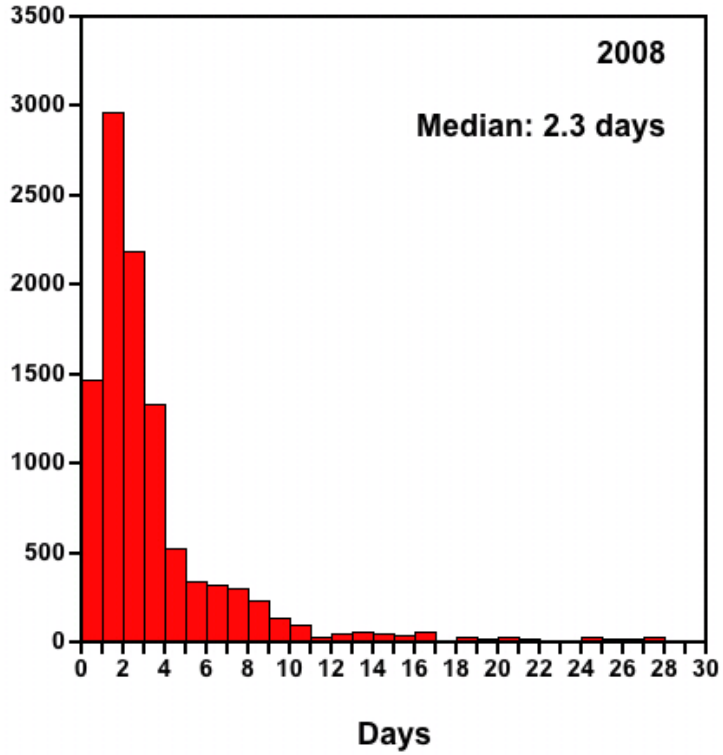
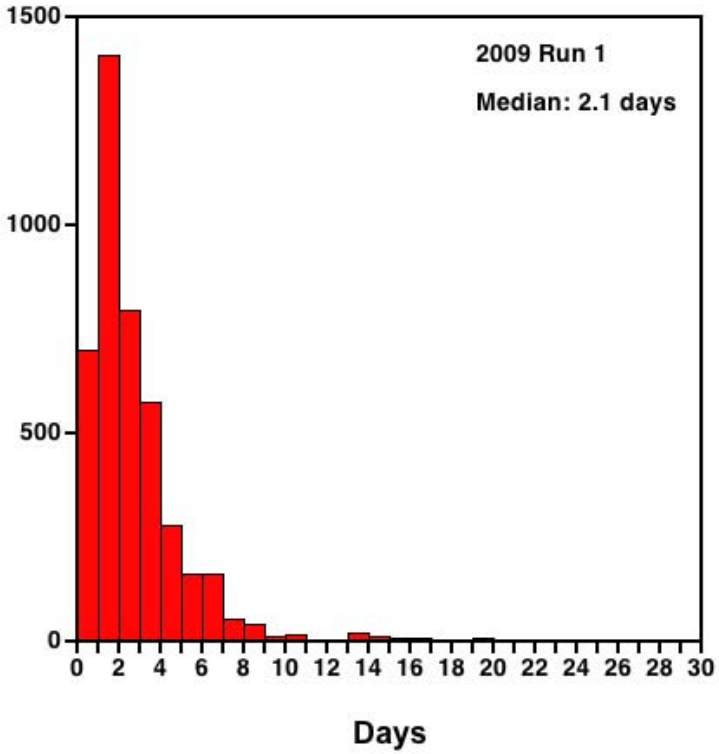
Sample turnaround





- 2008: Median 2.3 days, >80% within 5 days
- 2009 Run 1: Median 2.1 days, >85% within 5 days

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Lilly Proprietary Charges

- 2008: $783,000
- 2009 Run 1: $445,000

- ~90% for internal drug discovery

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Intellectual Property

- APS – New User Agreement
  - "USER may elect to obtain the entire right, title and interest in any patent application … on a(n) Invention and in any resulting patent …. If USER wishes to elect title to the … Invention, a notice of election should be submitted …."
- Diamond Light Source
  - "DLS … hereby assigns to the Customer the Intellectual Property Rights in the Results."
- Canadian Light Source
  - "CLSI hereby assigns to Lilly all Intellectual Property Rights to the Work Product…."
- Difference: at APS default is to the government

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Motivation

- Modern synchrotrons are superb technical instruments
- Can synchrotrons be a routine analytical tool for industry?

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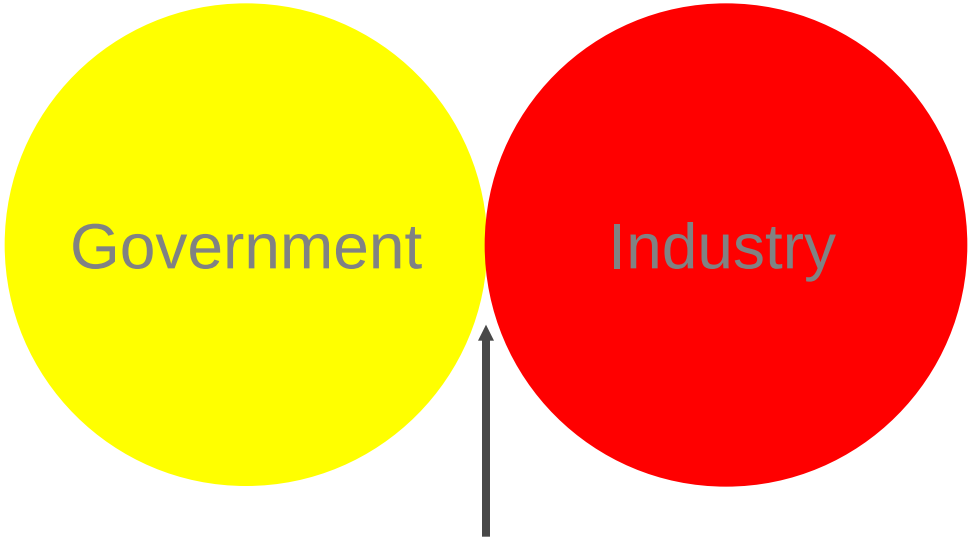
Intersection of Two Worlds



We are here

- Translators who speak the language of each are required

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What does Industry Want?

- Quality (successfully solve the problem)
- High value
- Rapid and easy access
- Retention of intellectual property
  - Particular issue in United States
- Reliability
  - Technical
  - Organizational
- Compatibility with their existing operations

- These requirements are interconnected

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Types of Industrial Analyses

- Part of process to develop product or solve problem
  - Pharmaceuticals: protein crystallography
- Characterization after project finished
  - Catalysts: x-ray absorption
    - Highly empirical science
    - Has been used for patent protection
- Hybrid: Environmental analysis

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Value of Analysis

- Part of process: high
  - Customers are insensitive to price (inelastic)
    - Can charge significantly more than cost recovery
  - Have essential need
  - Significant time pressure
  - Value can disappear overnight
    - If alternative methods are used

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Value of Analysis

- Characterization afterward: moderate to low
  - Sensitive to price (elastic)
  - Sometimes viewed as luxury
  - Can be important for future development, even if not immediate need

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Time Frame

- General conclusion from US and Japan
- Desired time from inquiry to delivered results: ~4 weeks

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Qualitative/Semi-quantitative Approach

- Often industry only needs to know the answer
- Level of detail can be less than for publication

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Man vs. Machine in R&D

- People (researchers) solve problems
- Analytical instruments provide the data

- The greatest resources at user facilities are the scientists who use and operate it

- Emphasize the capabilities of the scientists as well as the machine

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Final Thought

- Modern technologies have the greatest impact when they are tightly integrated into the processes of research and development programs

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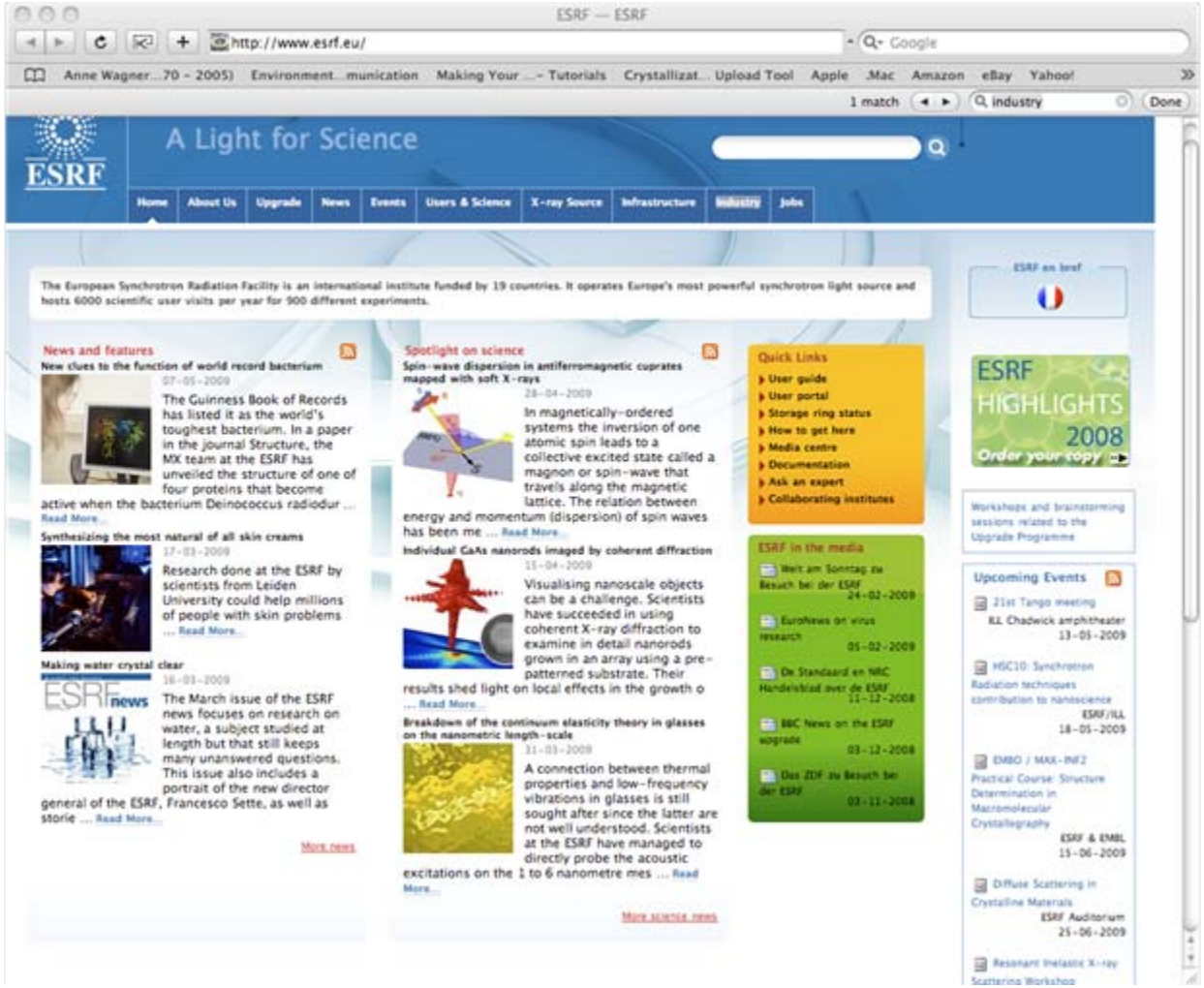
ESRF



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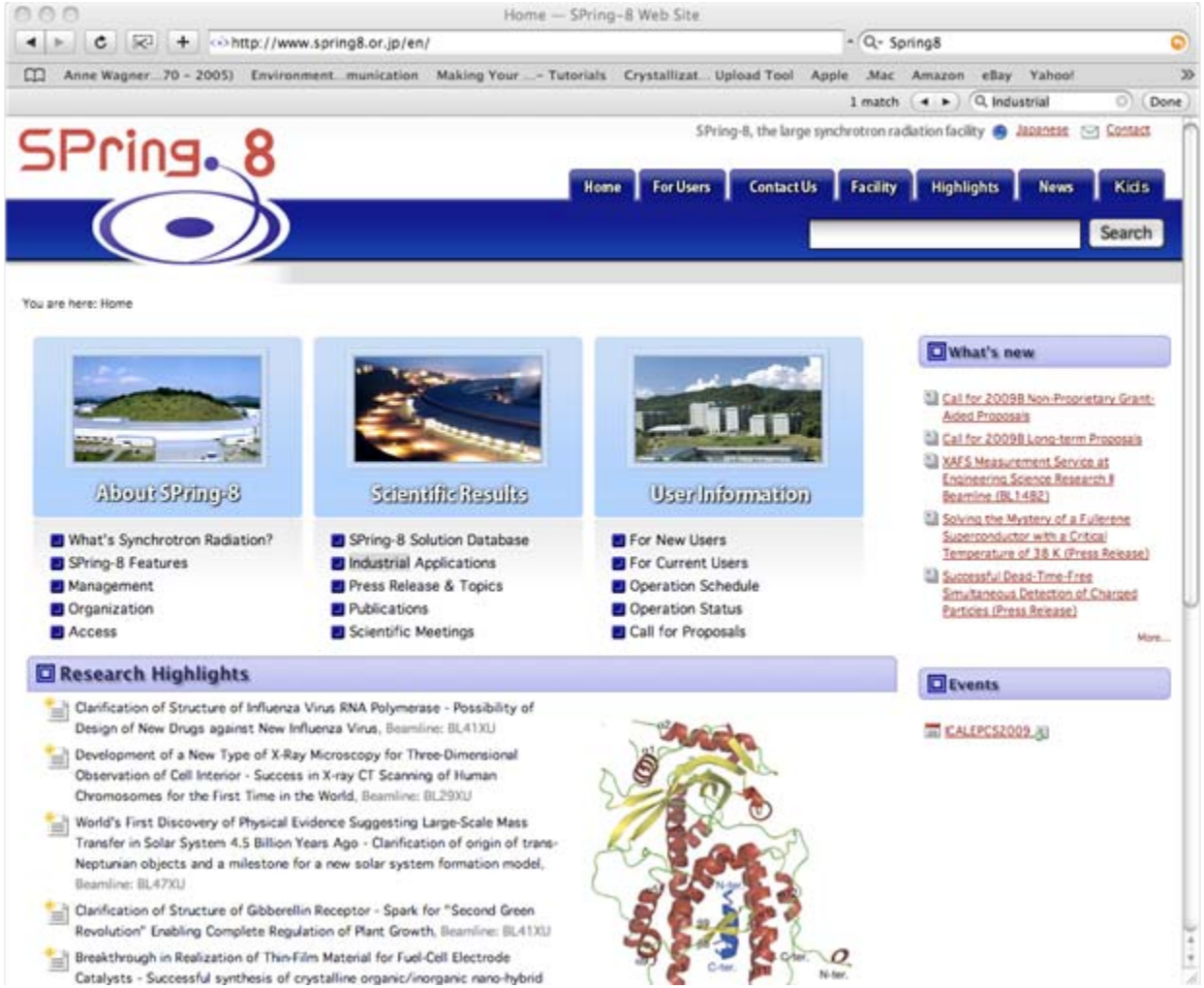

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Access: Example from the APS

- 1. Find a beamline that is suitable for your work

Scientific interface at synchrotron

- 2. Register with the APS User Office
- 3. Apply for beamtime

Eliminate proposals?

- 4. Make sure the sponsoring institution has a user agreement with the APS

Legal

- 5. If needed, establish a user account to pay for supplies and services
- 6. Arrange (well in advance) for delivery of samples/materials
- 7. Complete all required training immediately upon arrival

Economics

- Synchrotrons are expensive to build and operate
  - Require more corporate resources than available
    - IBM built their own, but gave it to the US after several years
  - Financed by governments for benefit of country
- Synchrotrons are the least expensive source of radiation on a per photon basis (cost per photon)
- Economy of scale

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Road to Success

- Provide easy access to synchrotron
- Effective communication and marketing
- Service to user (customer)
- Meet government and industrial expectations
- Creativity
- Continued investment in beamline and personnel

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