IMCA-CAT

A *production facility* for diffraction data

Charles A. Lesburg

IMCA Chairman *emeritus*

Senior Principal Scientist, Schering-Plough

What is IMCA?

- Industrial Macromolecular Crystallographic Association
  - Abbott, Bristol-Myers Squibb, Johnson & Johnson, Lilly, Merck, Novartis, Pfizer, Schering-Plough
  - Global companies with multiple sites worldwide
- Funds and oversees operations of IMCA-CAT (APS sector 17; ID & BM)

Goal: use structural data to aid discovery of new medicines

IMCA contribution to APS Sector 17

- Conceived in 1980s
- IMCA officially formed in 1990

- Capital timeline
  - design and construction of Sector 17 (ID & BM; 1990-1996)
  - 17-ID first light July 1996
  - 17-BM first light October 1996
  - 17-BM upgrade in 2005-2006 (“to theoretical maximum”)
  - 17-ID upgrade (late 2008-early 2010)
- Financial investments
  - Over $15M spent on beamline construction and improvements
    - $5M on current 17-ID upgrade
  - Approx. $15M spent on Sector 17 operations since 2000

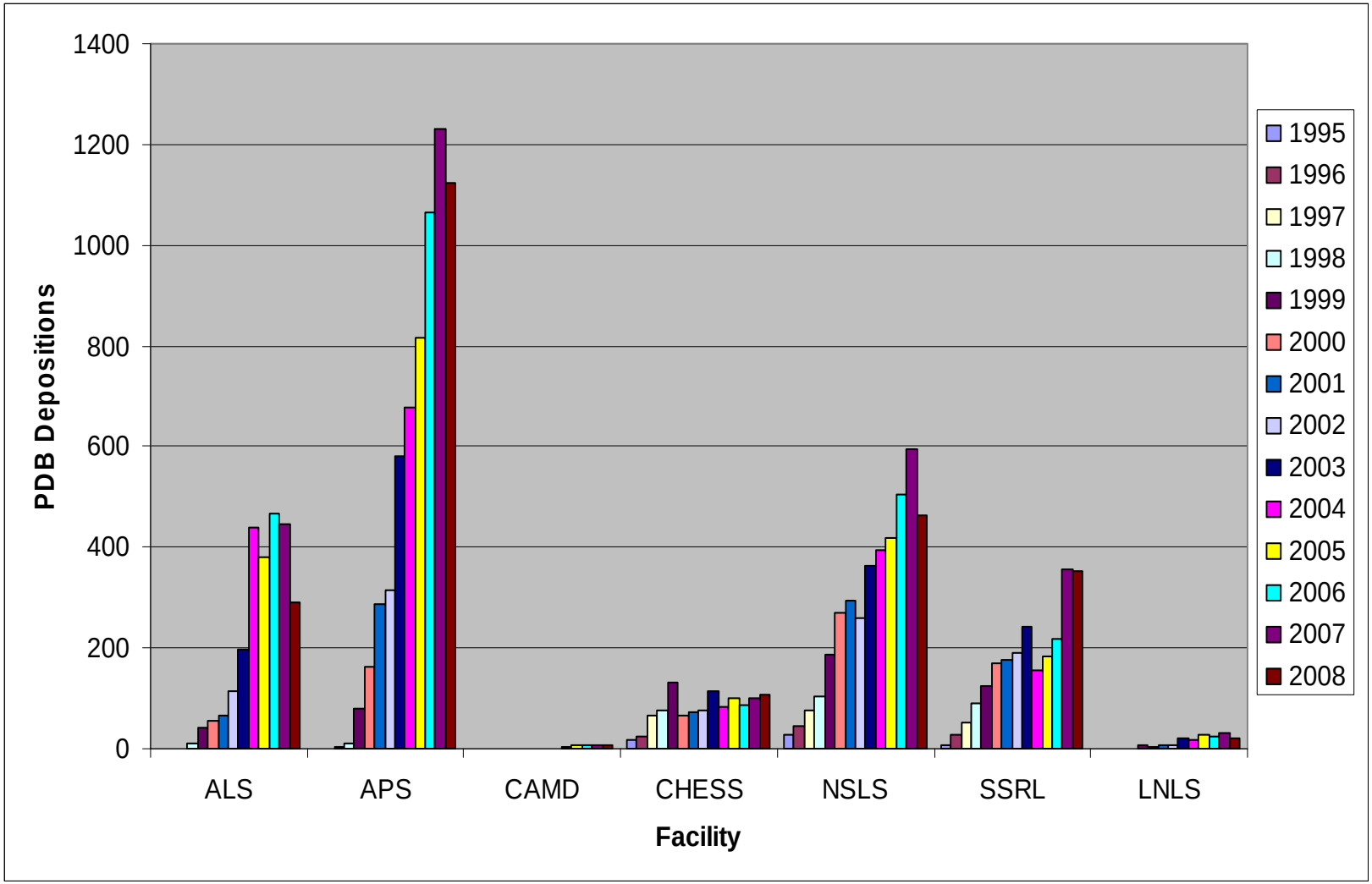
What do we do?

- Structural biology (10s of structures annually)
  - structural basis of biological interactions
    - protein:ligand, protein:protein interactions; epitope mapping of biologics
  - structure/function relationships
    - conformational states
- Structure-based drug design (100s-1000s)
  - improve intrinsic compound:target affinity
  - improve physicochemical and PK properties
  - improve intellectual property (IP) status and coverage
  - selectivity (minimize off-target effects) or pan-selectivity (resistance)
- Fragment-based drug design (high 100s-1000s)
  - complementary to high-throughput screening
  - find new chemical starting points
    - improve diversity of lead molecules
    - inspire chemistry not found in internal compound libraries
    - improve phyiscochemical and PK starting point
    - improve ligand efficiency
    - improve IP status and coverage

IMCA Member Needs

- Typical
  - High quality data
  - Beamline stability
  - Intense source
  - Tunable energy
  - Robust equipment
  - Small (“sizable”) beam
- Increased Focus
  - Guaranteed frequent access
  - Rapid data turnaround
  - Robust fault recovery
  - ***High capacity***
  - ***High data rate***
  - ***Proprietary use***
  - ***Cost-sensitivity***

Why APS?


1400
1200
1000
800
600
400
200
0
PDB Depositions
ALS
APS
CAMD
CHESS
NSLS
SSRL
LNLS
Facility
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008

Need for Speed

- IMCA-CAT productivity: 3500 datasets (2005)
  - 1.5 beamlines operational (extrapolate to ~4600 ds)
- 17-ID fully subscribed by IMCA members in 2007
- 1000s of datasets per company needed annually
  - Requires beamline investment:
    - stable and intense X-ray source
    - rapid detectors
    - sample changing automation
    - robust sample alignment
- Proprietary data collection essential
  - IMCA members contribute >$1M annually in prop. fees
  - Represents majority of APS proprietary use
  - Must be cost-competitive with (global) alternatives

Investment in Rapid Data Collection (1)

- Increase data collection rate
  - PILATUS 6M detector purchased (~$1.8M)
- Increase sample changing rate

PILATUS 6M Detector

- First large-format PAD for macromolecular crystallography @ APS
- Prototype running at Swiss Light Source for 2 years
- Typical dataset ~2 min
  - 10-12 min with current CCDs
- Advantages
  - **simplification** of endstation controls: shutterless operation
  - **simplification** of parameters: distance, frame width, sample orientation
  - **data quality improvement**: minimization of radiation decay
  - **increased capacity**

Large aperture: 431 x 448 mm^2
Readout: up to 12 Hz
Low noise
Typical data collection:
180° total width (0.2° x 900 frames)

Challenge: Maintain data flow @ ~50 GB/hr

Investment in Rapid Data Collection (2)

- Improvement in sample exchange (~3 min)
  - paying for closed shutter!
    - proprietary fee
    - capacity
  - saving 30 sec → 10% throughput increase
  - saving 60 sec → 23% throughput increase
  - Planned improvements to sample changing
    - no delay in sample exchange
    - better/faster sample centering and alignment
- Can acquire data on 180 samples without intervention (~12-16 hr capacity)
- Need to maintain sample success rate
  - Hardware: approaching 100%
  - Autocentering/sample prep: >95%
    - challenge: eke out last few %

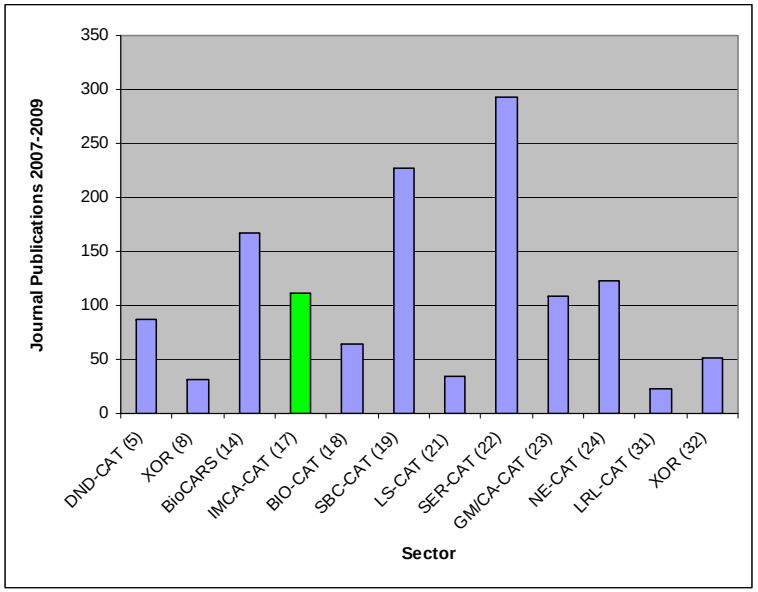
Confidentiality

- Consistent with proprietary data collection, need to maintain intellectual property
- IMCA members must have data protected from each other and from the larger community
- Extra pressures on IMCA-CAT staff on design of software and processes
  - data flow
  - sample logistics

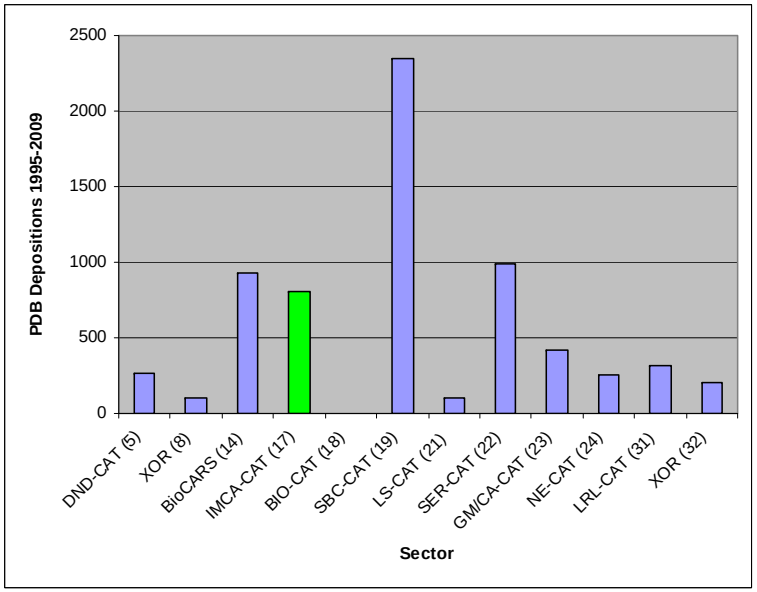
Cost-sensitivity

- Ongoing efforts to maximize value
  - minimum cost per dataset
    - proprietary data collection fee
    - operational cost
    - sample shipping
    - actual data collection/management
  - maximize benefits
    - rapid sample turnaround time
    - data quality
    - accessibility of small samples
- Development limited to what will directly improve value
  - remote access
    - minimizes travel and out-of-office costs (members)
    - allows for rapid troubleshooting (staff)
  - mail-in
    - monitored automated data collected
      - on-site (day) / remote (night)

Scientific Contribution



Source: BioSync 6/2009 (http://biosync.rcsb.org)



Source: APS Publications Database 6/2009 (http://www.aps.anl.gov/Science/Publications)

- IMCA-CAT is highly competitive with respect to journal publications and PDB depositions
- Medical Impacts
  - Drugs discovered with contribution from IMCA-CAT data collection

Example Medical Impacts

- Lopinavir (Kaletra®)
  - Abbott
  - HIV protease inhibitor
  - Stoll, V., et al., *Bioorg. Med. Chem. Lett.* **10**:2803-2806 (2002).
- Platensimycin
  - Merck
  - interferes with batcterial fatty acid synthesis
  - no cross-resistance to other key antibiotic-resistant strains tested, including methicillin-resistant S. aureus, vancomycin-intermediate S. aureus and vancomycin-resistant enterococci
  - Wang, J., et al., *Nature* **441**:358-361 (2006).
- Hepatitis C Virus NS5B Polymerase Inhibitors
  - Pfizer
  - Multiple inhibitor binding sites
  - >130 structures in 15 months; drove many series to nM potency; ongoing effort
  - Pfefferkorn et al., *Bioorg. Med. Chem. Lett.* **15**:2481-2486 (2005).
- Insulin Receptor
  - CSIRO
  - McKern, N.M., et al., *Nature* **443**: 218-221 (2006).

Academic/Industrial Partnerships

- Ongoing efforts
  - GUP
    - 2005/6 17-ID ~100% subscribed, reduced when other beamlines became available (e.g. GM/CA)
    - expect high level after 17-ID upgrade complete
  - Sample centering
    - collaboration with Purdue, GM/CA, SBC
  - Structural Genomics Involvement
    - SGC/Toronto
  - Structural Genomics/FBDD technique development
    - Univ. of Toronto
  - Structural Biology
    - University of Kansas
- Opportunities for partnerships with IMCA
  - Beamline controls
  - Sample handling/changing
  - Data logistics and processing pipelines

Contact Information

- IMCA Chairman: Dr. Travis Stams/Novartis
- IMCA-CAT Director: Dr. Lisa Keefe

- http://www.imca.aps.anl.gov