NSLS-II Proposal

How to Fund and Administer a Beamline(s)

The historical (and mostly current) model

* Individual ownership for each beamline
* Single owners or (more often) consortia (PRT, CAT, whatever) raise funds
* Design and build the beamline (with oversight)
* Administer and operate the beamline

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Is this the appropriate model for NSLS-II?

* One of the questions we should consider very early on
* Shared-ownership model has strengths and weaknesses
* Experience at IMCA-CAT (APS) is both typical and highly atypical
* Typical: need to staff, need to equip, need to evolve
* Atypical: committee governance, proprietary research, secure funding

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The View from Big Pharma

The most important point

* All pharmaceutical companies are not created equal

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The second most important point

* Each pharmaceutical company has a different approach to structural biology

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The most important point

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The third most important point

* I work for Merck (Rahway)
* Merck is a member of IMCA (APS sector 17)

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The IMCA Beam Line Model

IMCA membership

* Currently 12 shares
* Merck, Pfizer(3), P&G, BMS, GSK(2), 3DP, Lilly, Abbott, Schering-Plough
* Each share has an equal vote, equal financial responsibility

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The IMCA Beam Line Model

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IMCA was formed in the very early days of APS planning

* Each company paid dues for several years before beamline construction
* IMCA accrued a considerable bankroll before construction began
* Contracted with IIT (via CSRRI) for design and construction of beamline
* Appointed IMCA-CAT director with academic appointment at IIT

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IMCA today

* Still 100% funded by member companies
* Operating both ID and BM lines at near 100% usage

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IMCA Operations

Two beamlines

* ID - ADSC Q210 + CrystalLogic + MSC Actor robotics sample changer
* BM - Mar 165 + MarDTB
* Spare Mar 165 as back-up

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Finances

* 2003 dues for each company $150,000
* Total budget $1.8M - $1.4M operations, $0.4 accrued for upgrades
* Each member company gets ~12 ID and ~15BM days per year
* ~$10,000 a day (if you are using both beamlines)

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Staffing

* Authorized 7-8 FTEs
* Hard keeping all of these positions filled - poaching from newer beamlines

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How is Big Pharma Beamline Usage Different from Academia?

The structures we study

* Proteases
* Kinases
* Nuclear receptors

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All we do is bind and grind

* True - once we have a crystal system established, we do look at many complexes
* False - this is trivial
* The easy problems we do over and over and over
* The demanding problems we also do over and over and over

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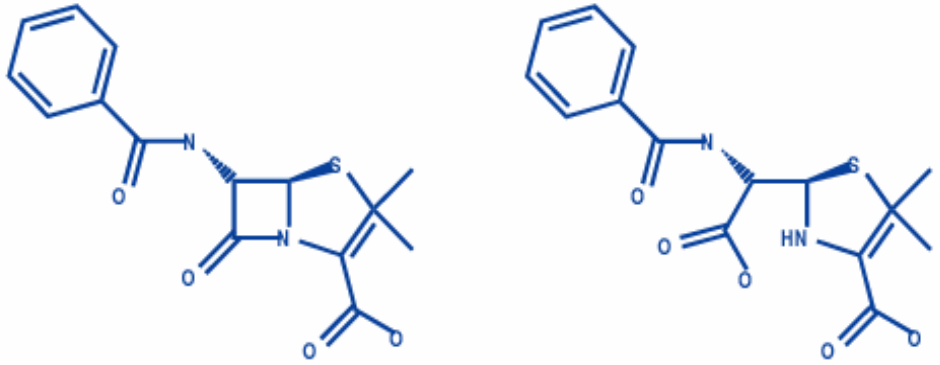
The reality

* Our mission is to expedite medicinal chemistry
* A structure that kills a program is as useful as one that moves it forward

β-lactamases

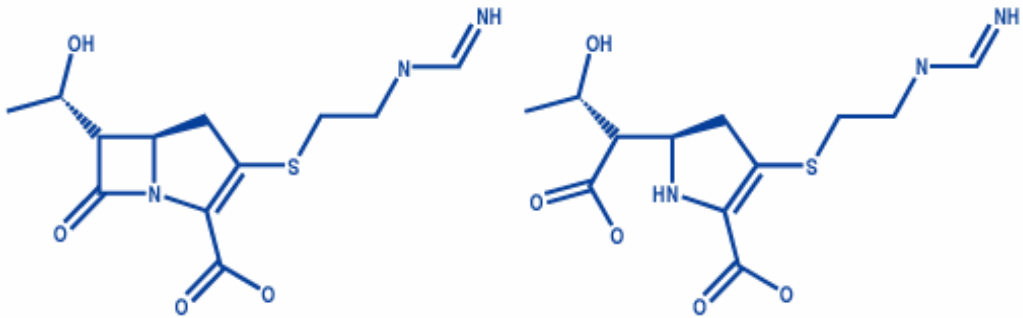
Resistance to antibiotics

Strains of bacteria that have serine-beta-lactamase-mediated resistance to penicillin antibiotics are effectively treated with a combination therapy (Augmentin)



Penicillin G, active and inactivated forms

Our goal is to identify a metallo-beta-lactamase inhibitor than can be used in combination with a carbapenem antibiotic to treat resistant strains



Primaxim (imipenem), active and inactivated forms

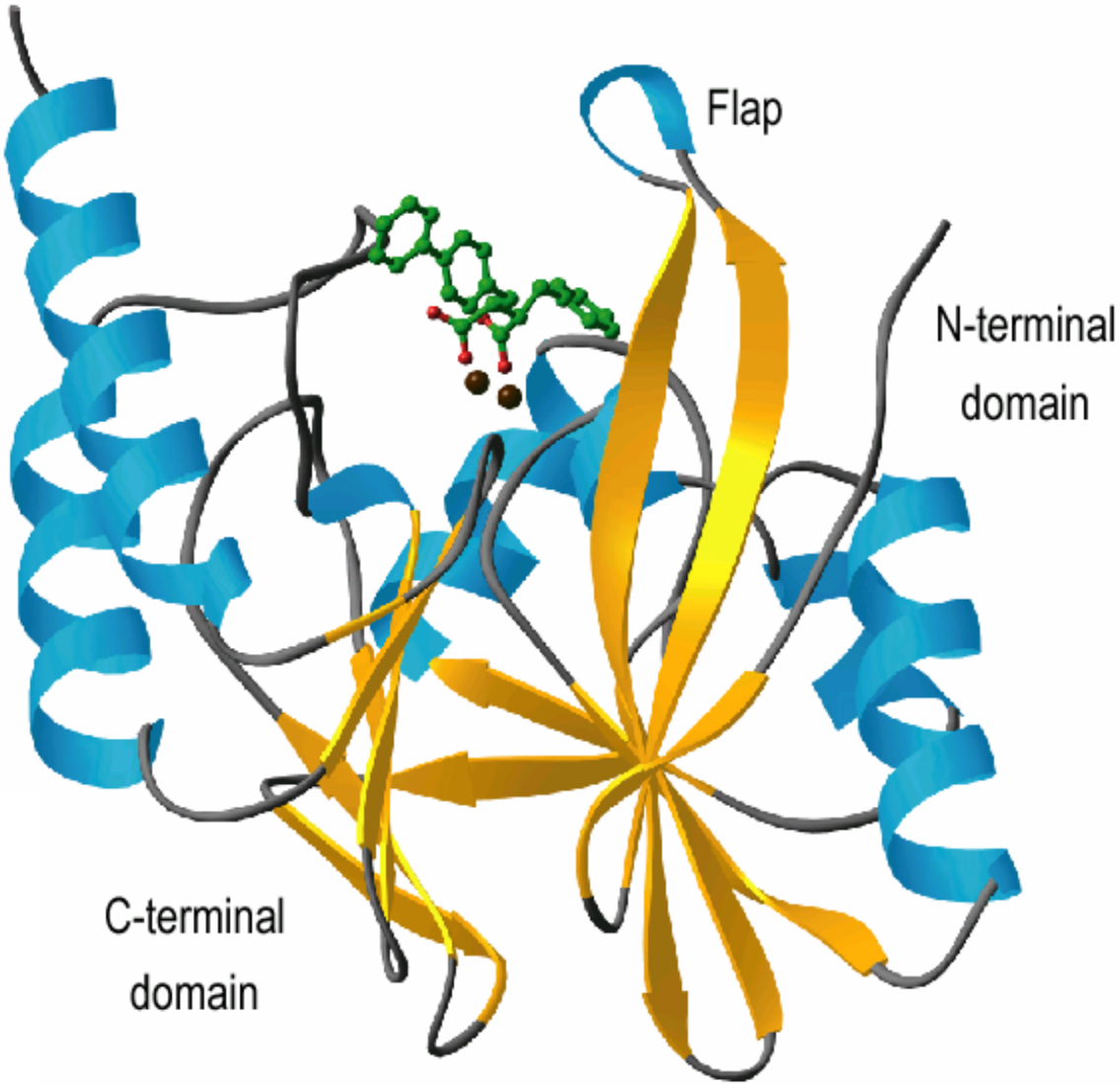
Metallo-β-lactamases

Overview of structure

The enzyme is composed of N-and C-terminal domains, with nearly identical topology

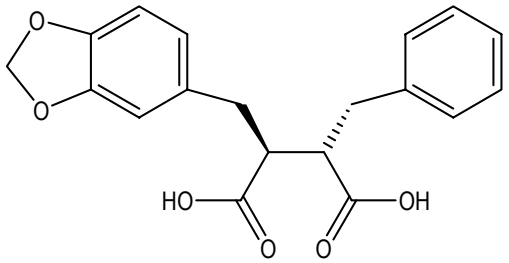
The active site, which contains two zinc atoms, is at the interface of the two domains

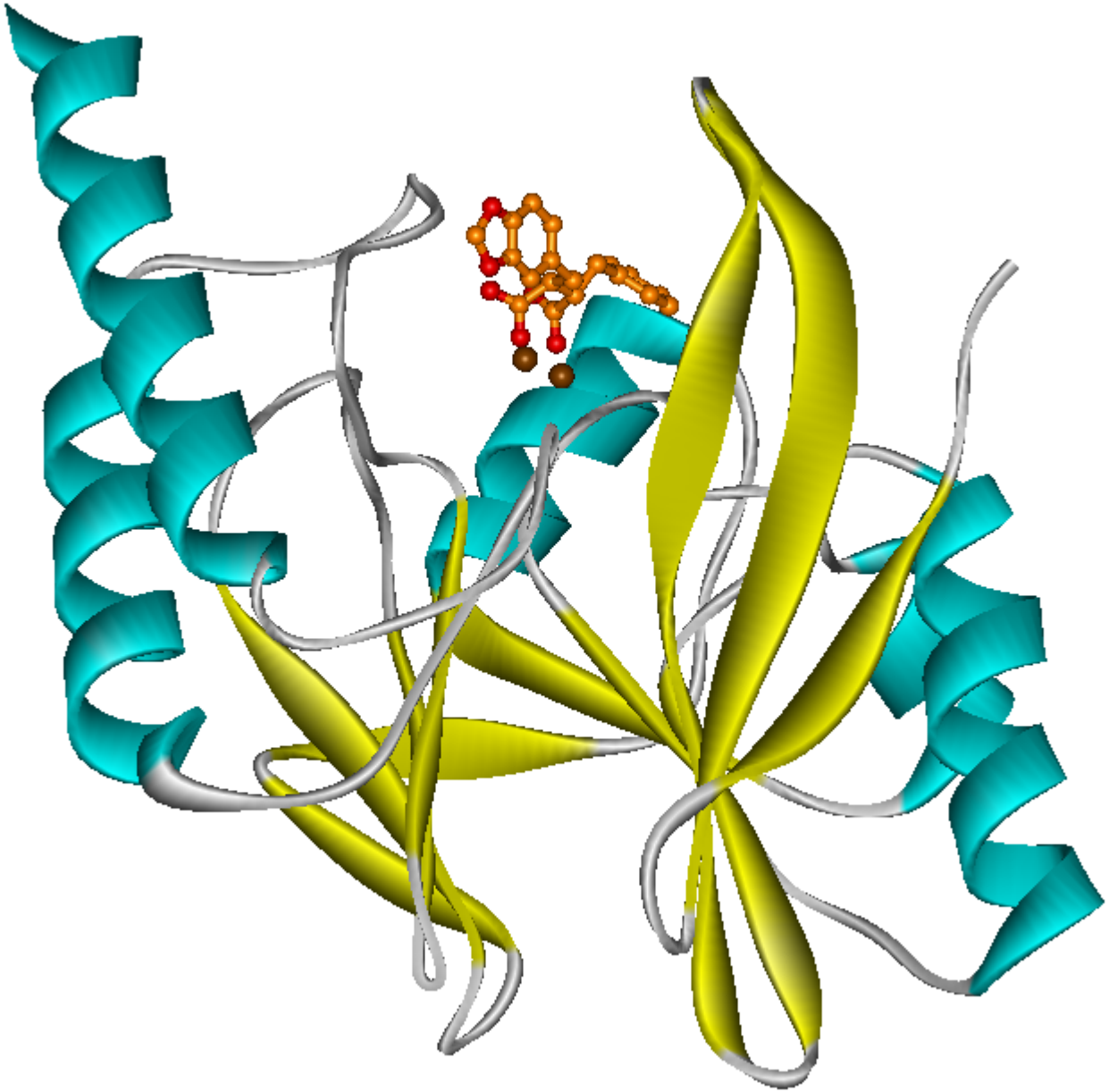
The Flap is a flexible b-ribbon with a hydrophobic inner surface that forms an interface with ligands



IMP-1 metallo-β-lactamase complexes

Compound C - Overview of binding

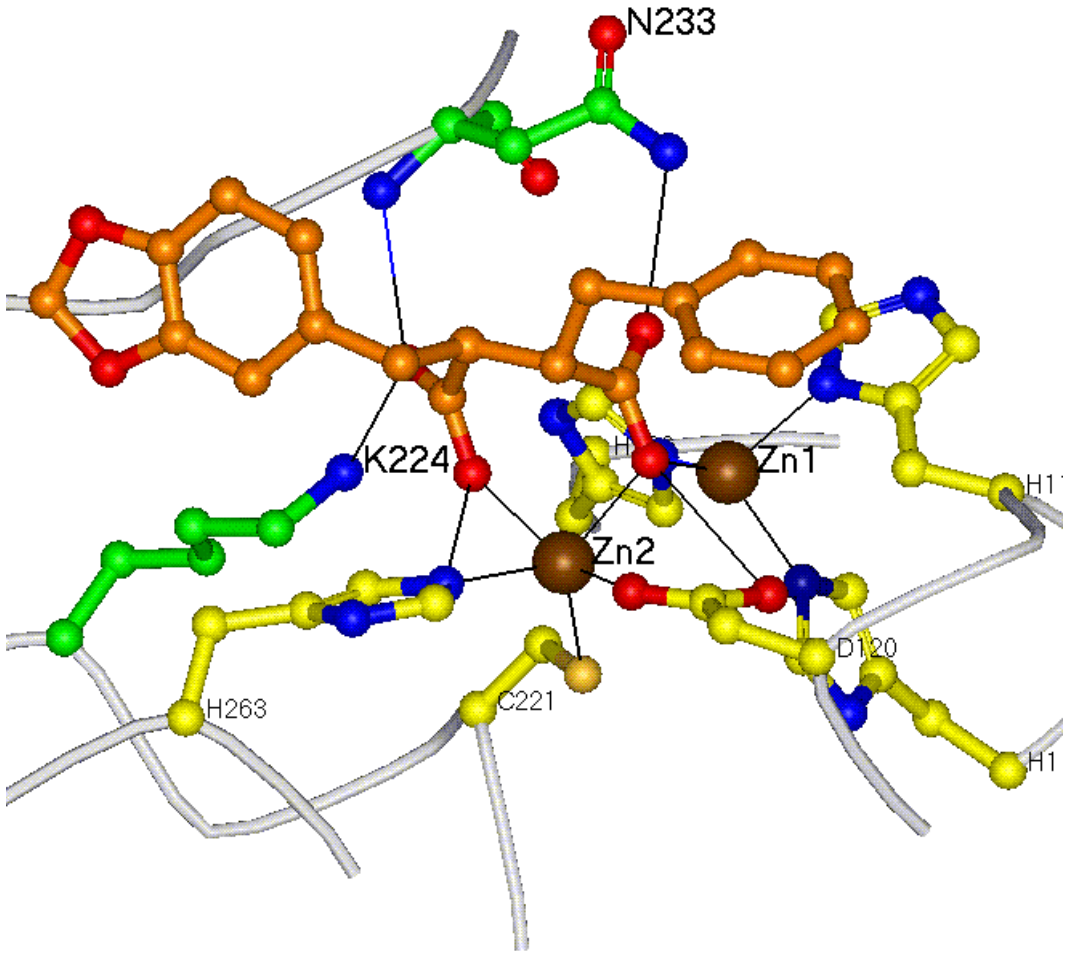




IMP-1 metallo-β-lactamase complexes

Compound C - Polar interactions

One succinate oxygen takes the place of the bridging water



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A second succinate oxygen
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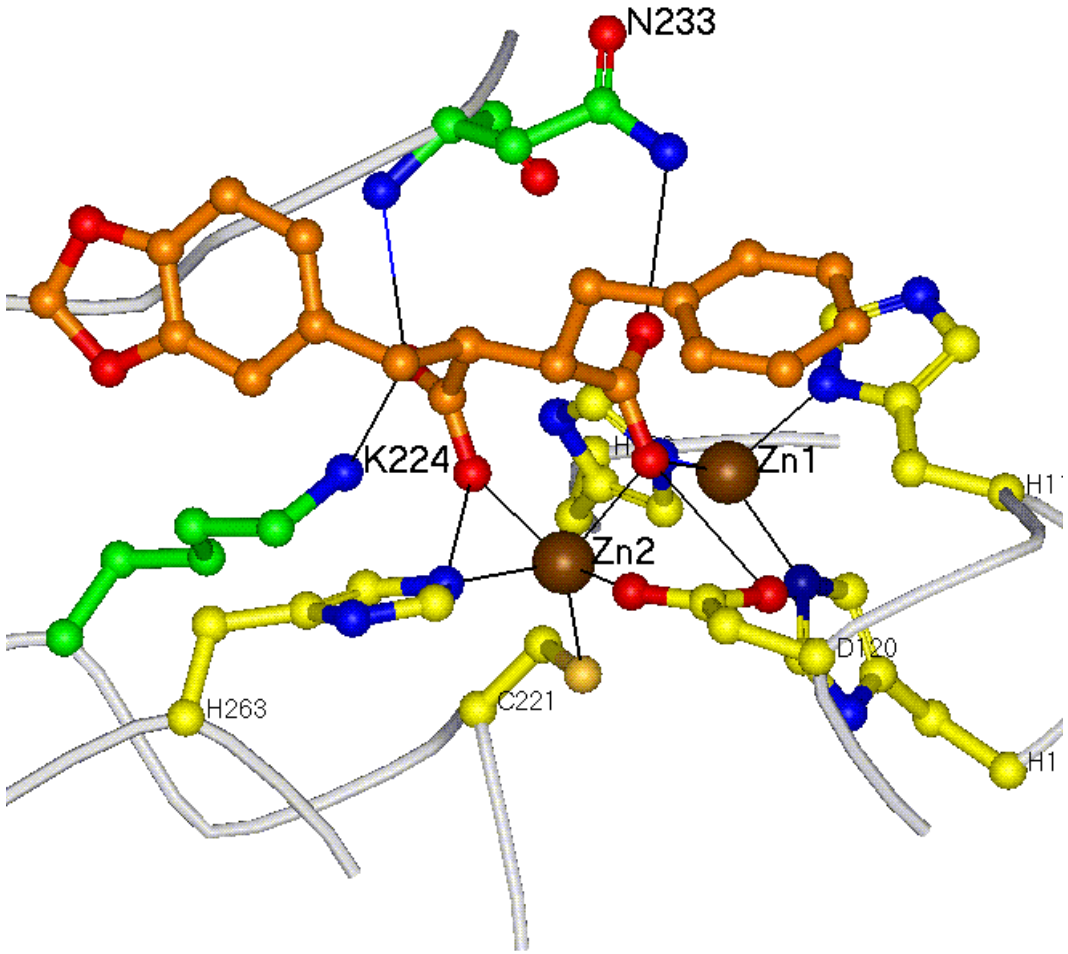

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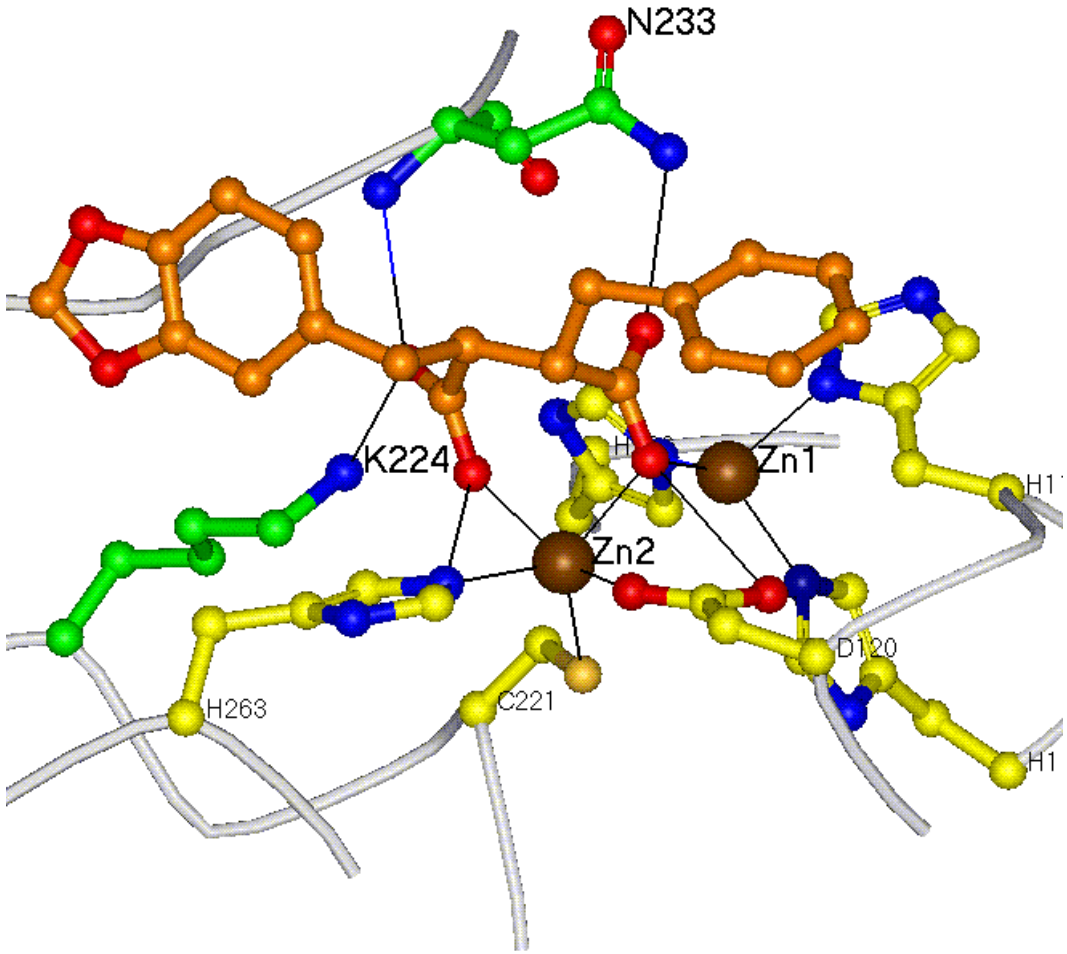
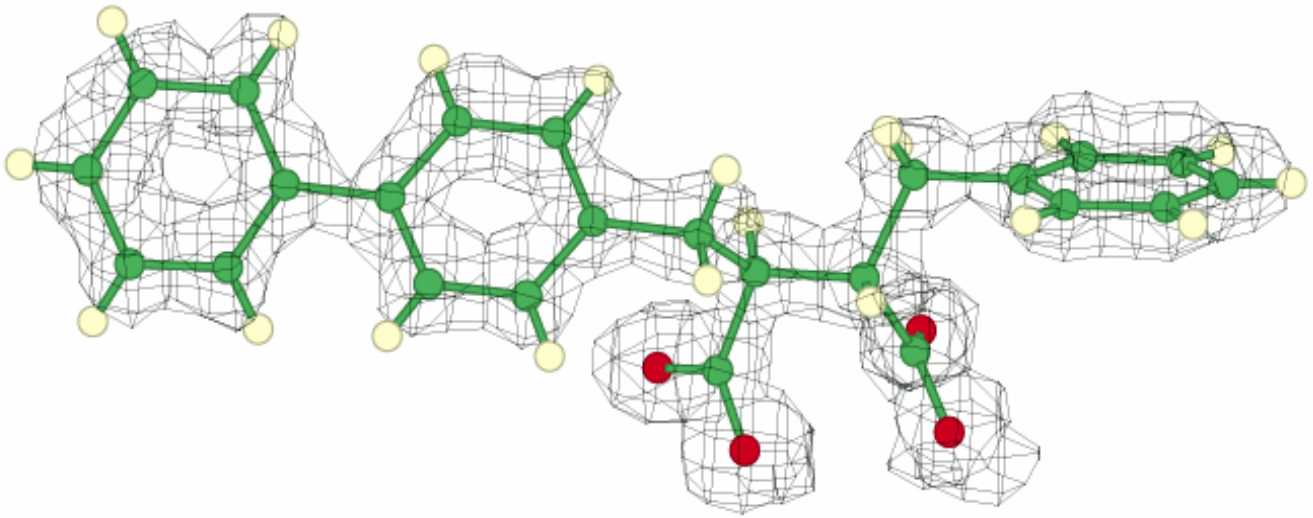
Residues Lys244 and Asn233
make key polar interactions
with succinate oxygens



IMP-1 metallo-β-lactamase complexes

Compound E - Fit of inhibitor to density



R(work) = 0.129

R(free) = 0.155

50.0-0.92 Ang. data

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IMCA Governance

Operational decisions are approved by a Supervisory Board

* Board meets 3-4 times per year
* Each share has one vote
* Board officers are elected annually (usually re-elected once)
* System was put together by 12 lawyers from the 12 original IMCA shareholders
* Pay close attention to your by-laws – they have far-reaching consequences

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Governance by committee is challenging

* Board members tend to focus intensely on IMCA issues during board meetings…
* …then forget about them until they come to collect data

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How Are We Different - Redux

Most of the work we do is proprietary

* Pay proprietary charges for our beamtime
* APS sets full cost recovery number (Ring operating costs/# of endstations)
* Currently ~$1550/8 hour shift = ~$9000 a day if you use ID and BM

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We don't publish at the same rate as academics

* Varies enormously from company to company
* GSK NC at one extreme - one Nature/Science paper after another
* 3DP at the other - a very secretive corporate culture
* Eventually most work will be published (deposited), but delays can be years

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We need to be accepted for what we are

* This has been an issue at APS in the past
* Less so under current management

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How Can Big Pharma Be Involved in the Proposal?

Deep pockets

* We have already demonstrated our willingness to put real money into beamlines
* Our need for beamtime will certainly not decrease, and may increase
* These are difficult financial times, and money is not easy to come by

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* Providing funding for NSLS-II is going to take some compelling arguments
* Proximity is probably not the best argument
* Rapid access and efficiency are better sells

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Disclaimer

* Not only do I not represent all of IMCA
* I don't even represent all of Merck