

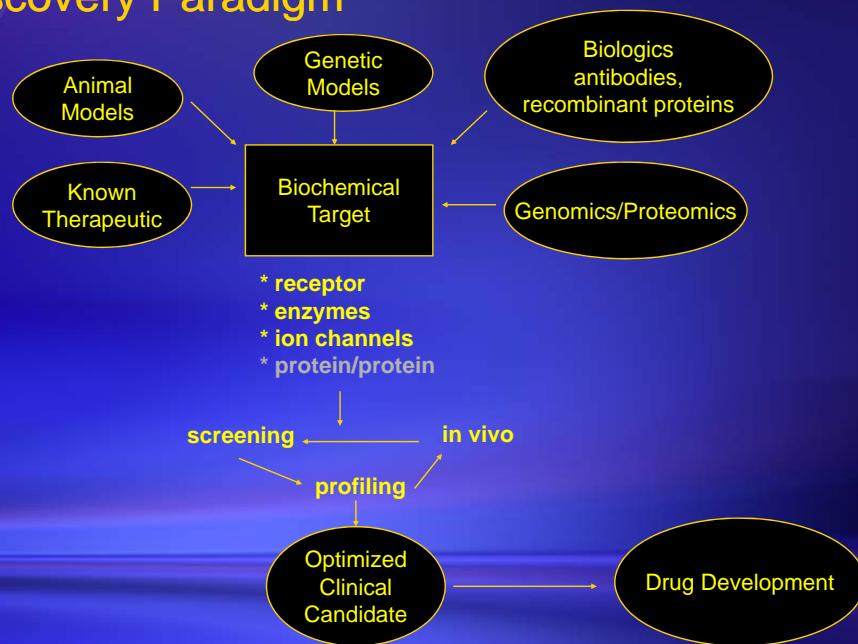
Innovation in Drug Discovery

Carl P. Decicco

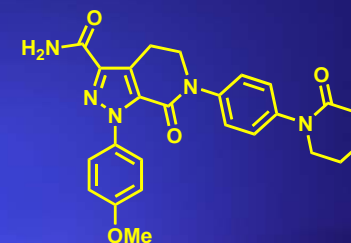


The Discovery of Apixaban: A next generation oral anti-coagulant

Mechanistic Approach - The Modern Drug Discovery Paradigm



Apixaban: Phase III clinical trials ongoing for deep vein thrombosis, acute coronary syndrome and atrial fibrillation.





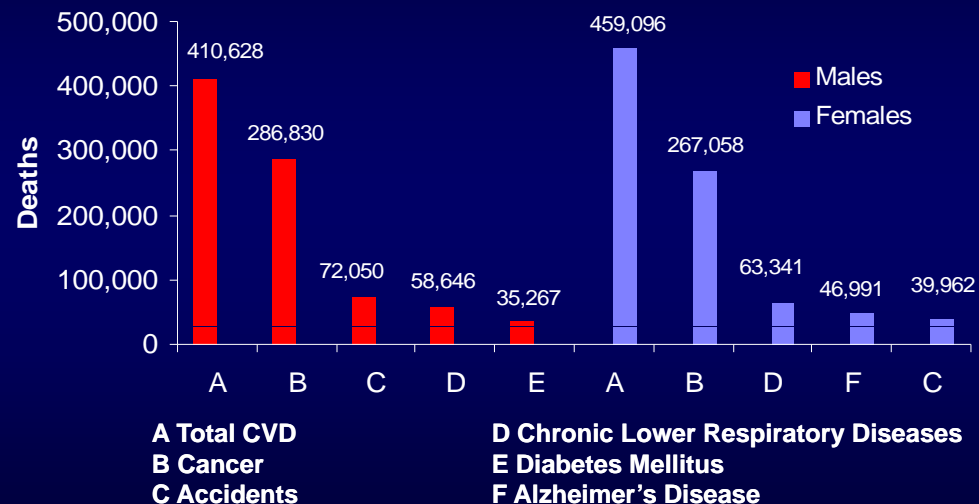
Serine protease inhibitor
 No "serine trap"
 No chiral centers
 Very potent and selective for FXa
 Excellent pharmaceutical properties

Apixaban

Factor Xa Discovery Program

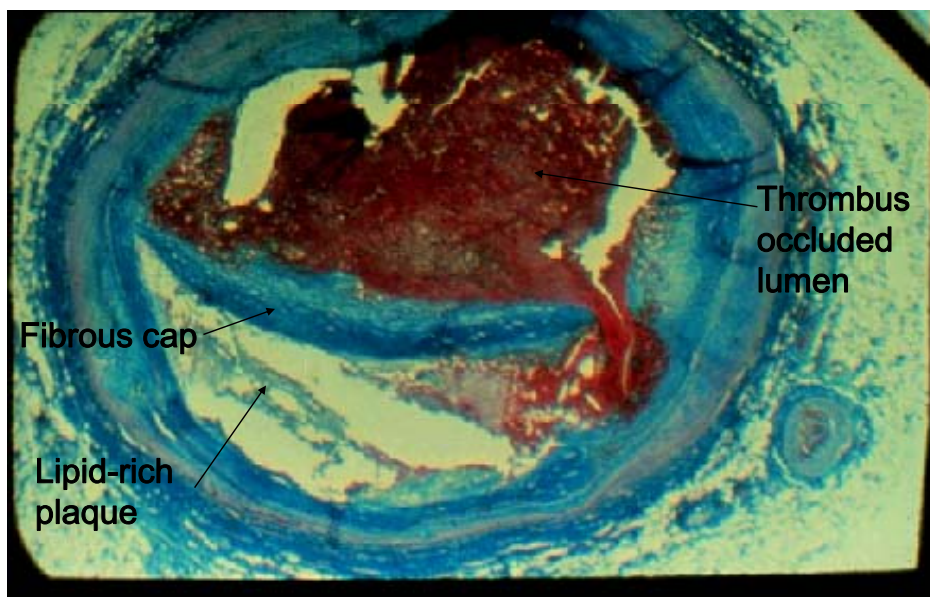
Innovative steps leading to the Discovery of Apixaban

The leading cause of death in developed countries:
 cardiovascular events, primarily due to thrombosis

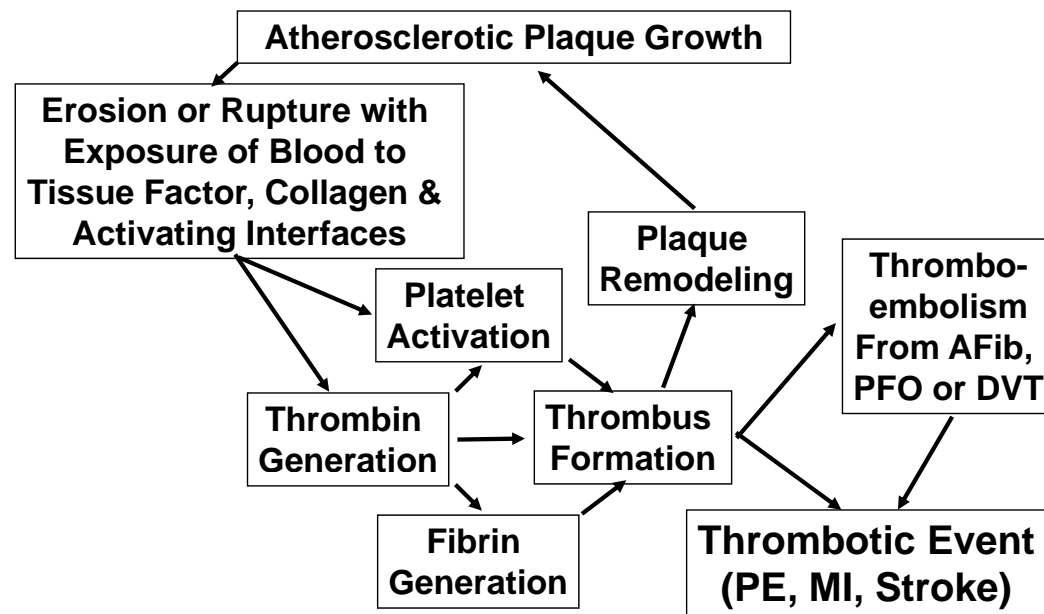


(United States: 2004). Source: NCHS and NHLBI.
<http://www.americanheart.org>

Human Atherosclerotic Plaque Rupture



Thrombotic Disease Process



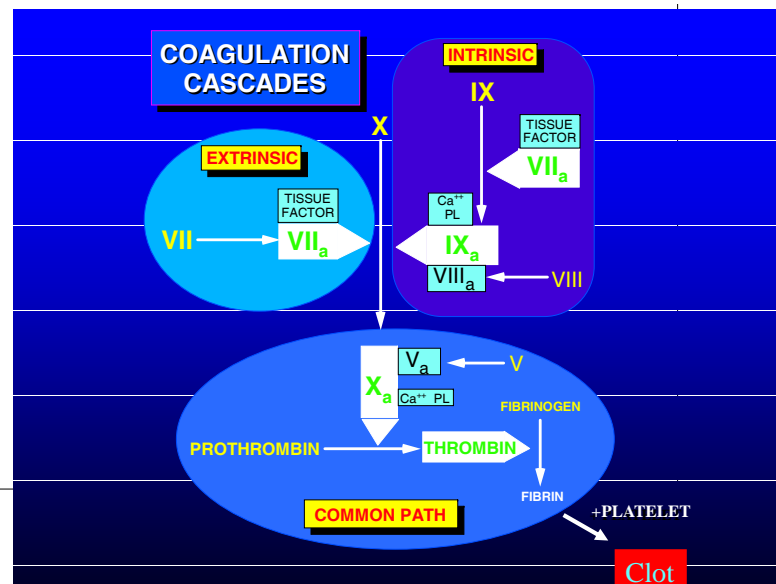
Current Orally Active Anti-thrombotic Drugs

- **Warfarin (Coumadin) – anticoagulant (vitamin K epoxide reductase)**
Reduces events in atrial fibrillation, cardiac valve replacement, venous thrombosis, pulmonary embolism, and post-MI
 - Narrow therapeutic index **limited by bleeding**
 - Requires dose **adjustment** and monitoring by INR
 - Response influenced by dietary vitamin K
 - Response varies greatly among different individuals, and may vary in an individual over time
 - Extensive interactions with other drugs
- **Aspirin – antiplatelet (cyclooxygenase)**
Reduces events in angina, ACS, PCI, TIA, CABG, carotid endarterectomy and post-MI or -stroke
 - Limited efficacy; improved in combination with clopidogrel
- **Clopidogrel (Plavix) – antiplatelet (P2Y12 receptor)**
Reduces events in ACS, PCI/stent, CABG, PAD, and post-MI or -stroke
 - Better efficacy than aspirin alone; improved in combination with aspirin

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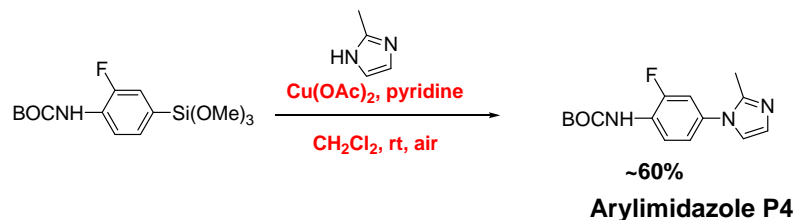
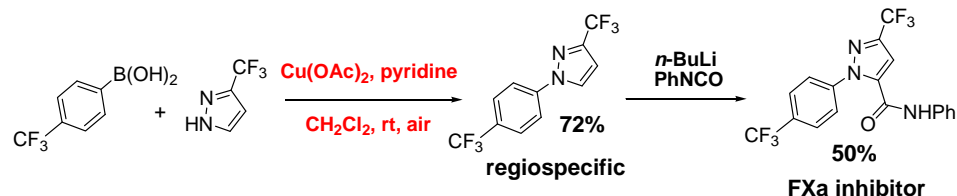
➤ **Unmet medical need for more effective, convenient, and safer oral antithrombotics**



Applications of copper-promoted C-Heteroatom cross-couplings in BMS/DuPont

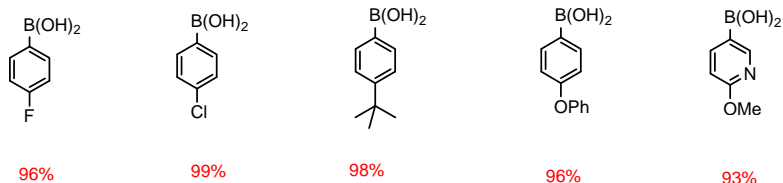
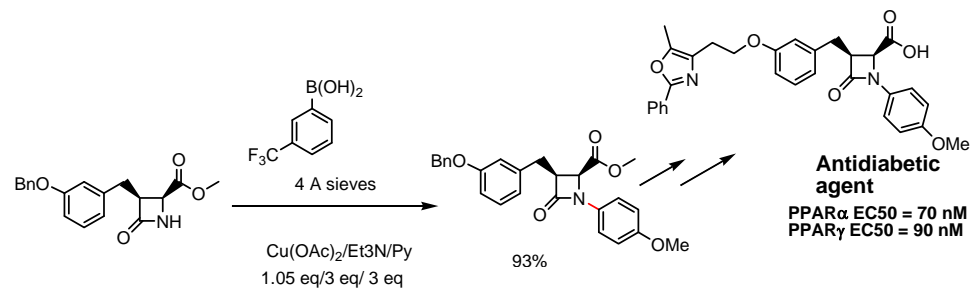
Factor Xa is an arginine-specific serine protease, as are all of the other Factor proteases and trypsin.

Applications in FXa inhibitor synthesis



Lam, Clark, Li unpublished

Application in anti-diabetic agent synthesis

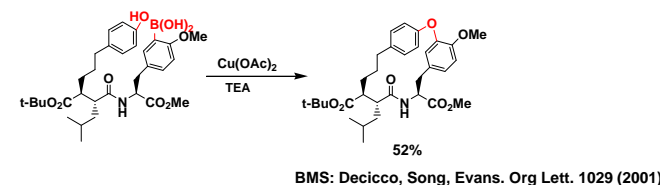


-Remarkable yield with no epimerization.
 α -Carbonyl activating effect is critical, α -acetal lower yield.

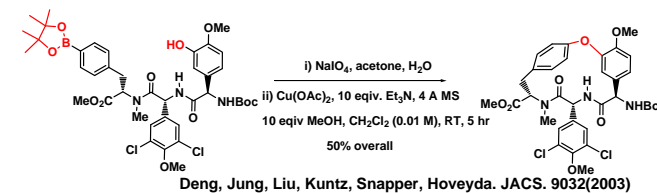
BMS: Wang, Devsathale, et al, BOMCL, 1939(2008).

Intramolecular O-arylation

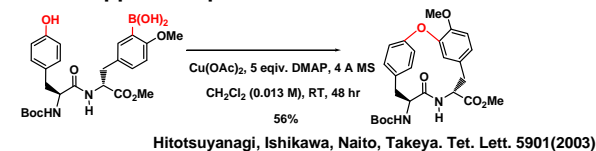
First Intramolecular O-arylation: Synthesis of metalloprotease inhibitors
 -other classical methods failed



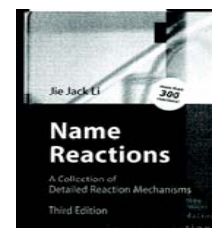
Total synthesis of Chloropeptin I
 -10 eq. methanol improves the rate and yield of reaction



Synthesis of L,L-cycloisodityrosines
 -5 eq. DMAP suppresses protio-deboronation



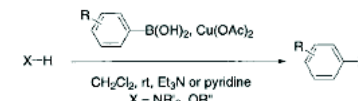
Patrick Lam, Director,
Hopewell Chemistry



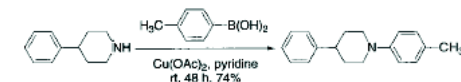
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Chan-Lam coupling reaction

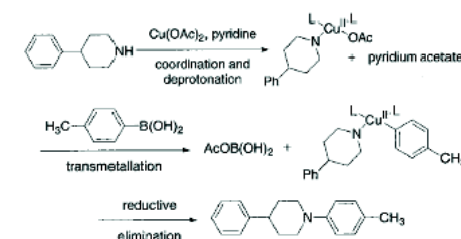
N-Arylation of a wide range of NH substrates by reaction with boronic acid in the presence of cupric acetate and either triethylamine or pyridine at room temperature. The reaction works even for poorly nucleophilic substrates such as arylamide.



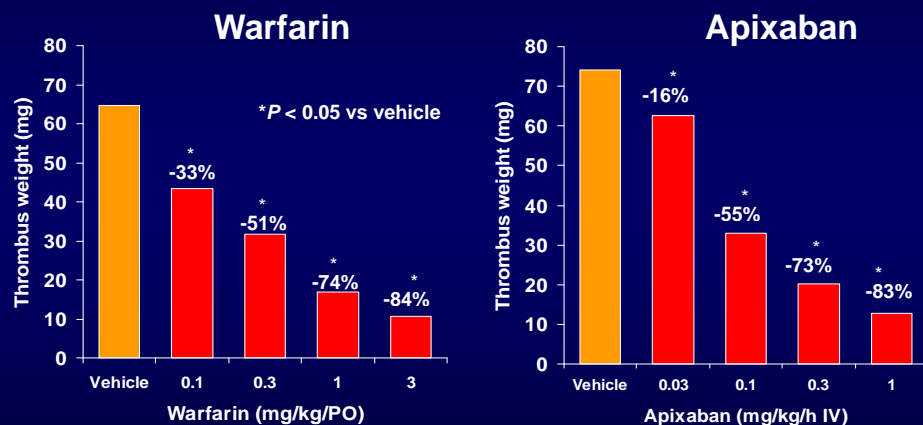
Example 1¹



Mechanism:

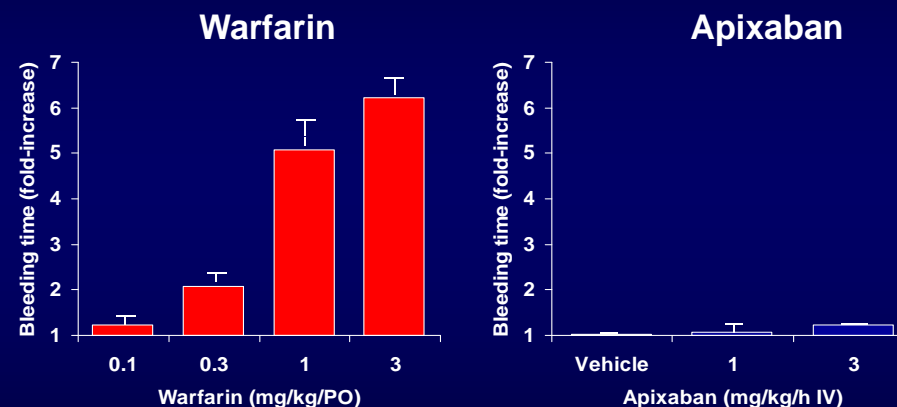


Antithrombotic Effects in DVT Rabbits

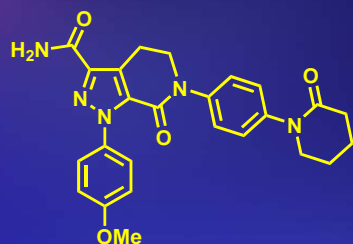


Wong, et al. *J Thromb Haemost.* 2008;6:820-829.

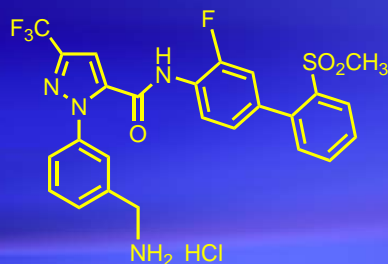
Bleeding Time Effects in Rabbits



Wong, et al. *J Thromb Haemost.* 2008;6:820-829.



Apixaban



DPC-423



Razaxaban

"This is an important point: neither biology nor chemistry would be served best by a development in which all organic chemists would simply become biological such that, as a consequence, research at the core of organic chemistry and, therefore, progress in understanding the reactivity of organic molecules, would dry out. Progress at its core in understanding and reasoning is not only essential for organic chemistry itself, but for life science as a whole. Life science needs an Organic Chemistry that remains strong." – -Albert Eschenmoser, 2008

FXa Acknowledgements

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Bruce Aungst

Janan Jona

Scott Grossman

Clinical trials

Rogelio Mosqueda

David Kornhauser

Michael Lassen

Bruce Davidson

Alexander Gallus

Graham Pineo

Jack Ansell

David Deitchman

Research Facilities



Lawrenceville, NJ

BMS Research Facilities



Wallingford, CT

Hopewell, NJ

