Innovation in Drug Discovery

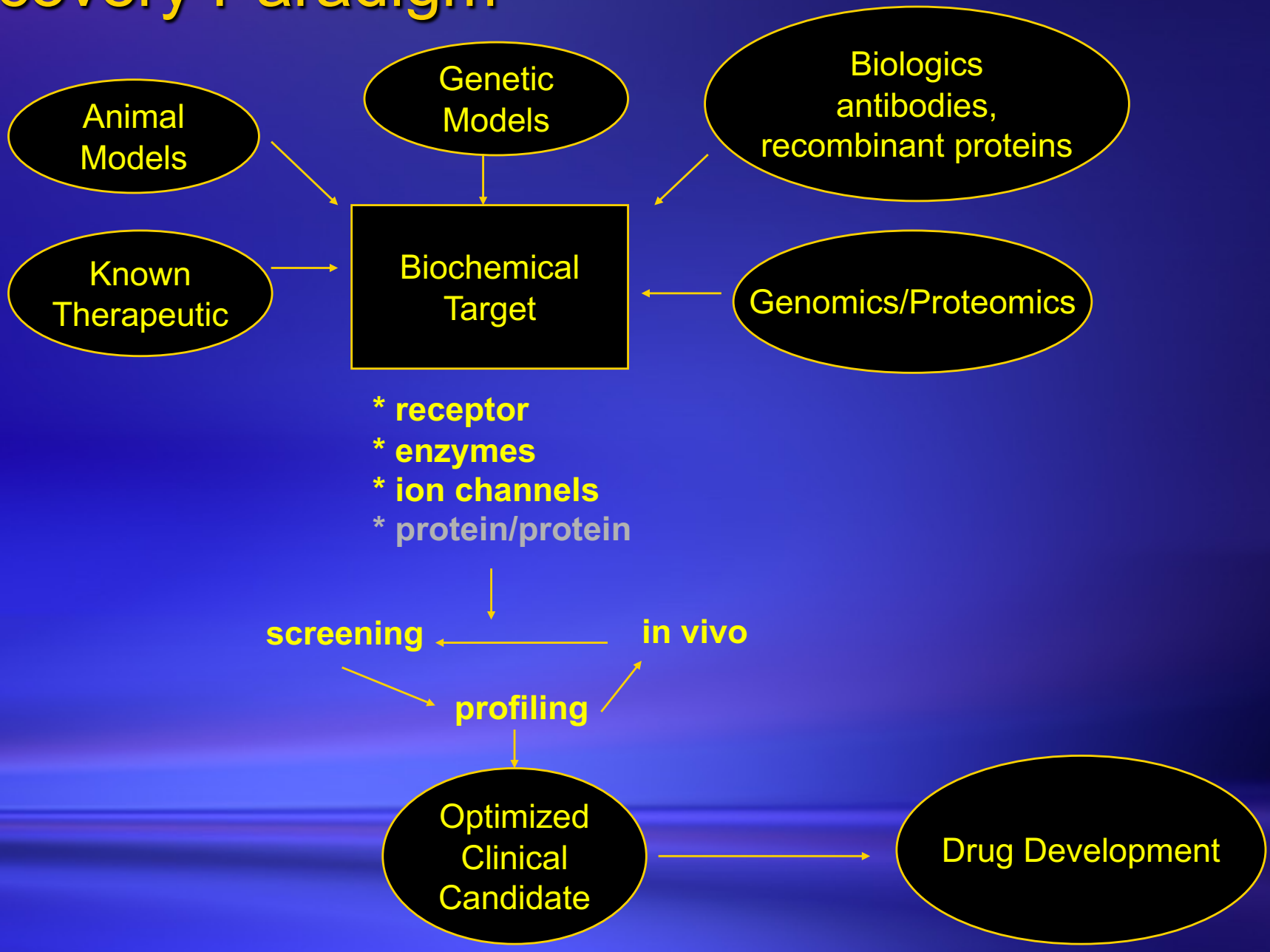
Carl P. Decicco

Bristol-Myers Squibb Company

1nm

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.



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Apixaban

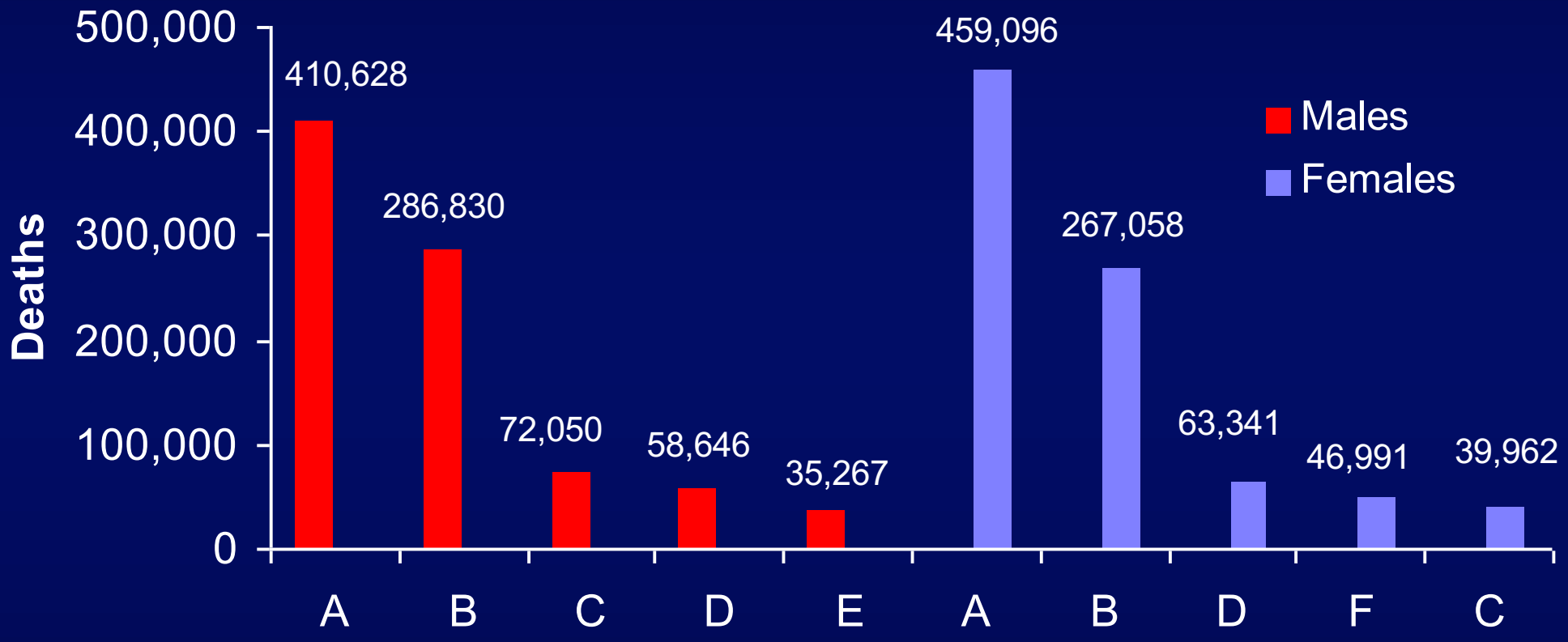
- Serine protease inhibitor
- No “serine trap”
- No chiral centers
- Very potent and selective for FXa
- Excellent pharmaceutical properties

Factor Xa Discovery Program

Innovative steps leading to the Discovery of Apixaban

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

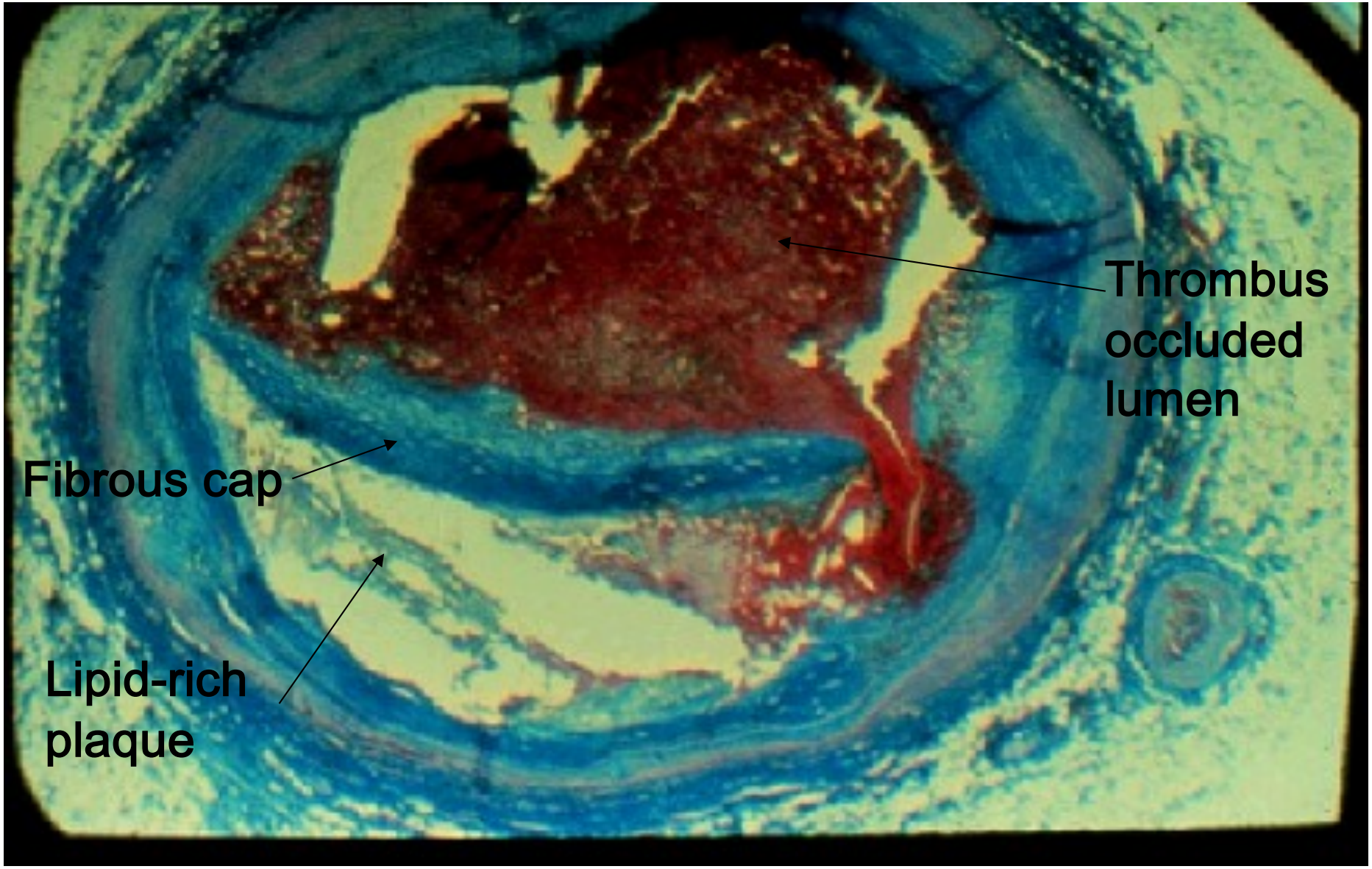


A Total CVD
B Cancer
C Accidents
D Chronic Lower Respiratory Diseases
E Diabetes Mellitus
F Alzheimer's Disease

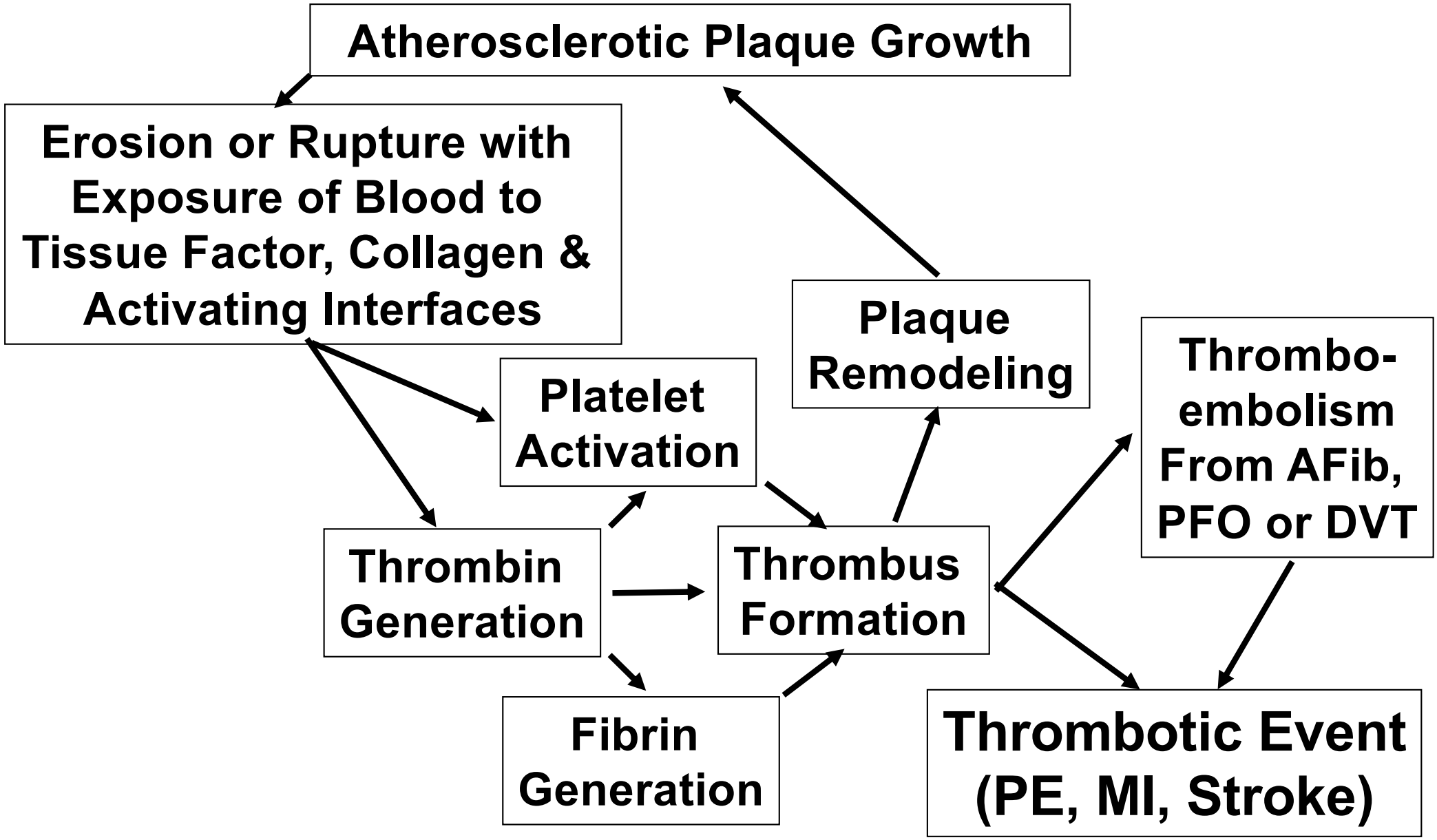
(United States: 2004). Source: NCHS and NHLBI.
http://www.americanheart.org

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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

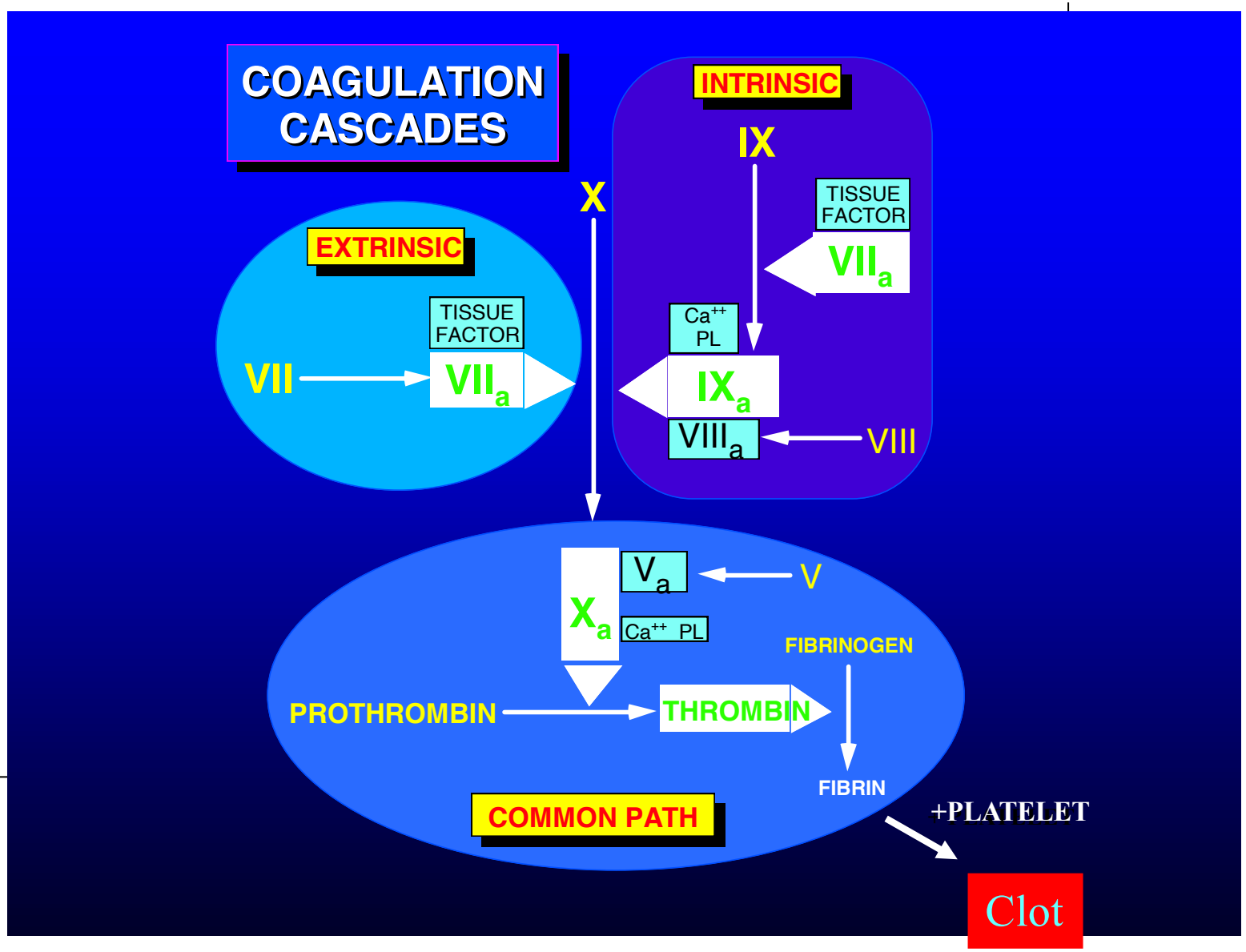
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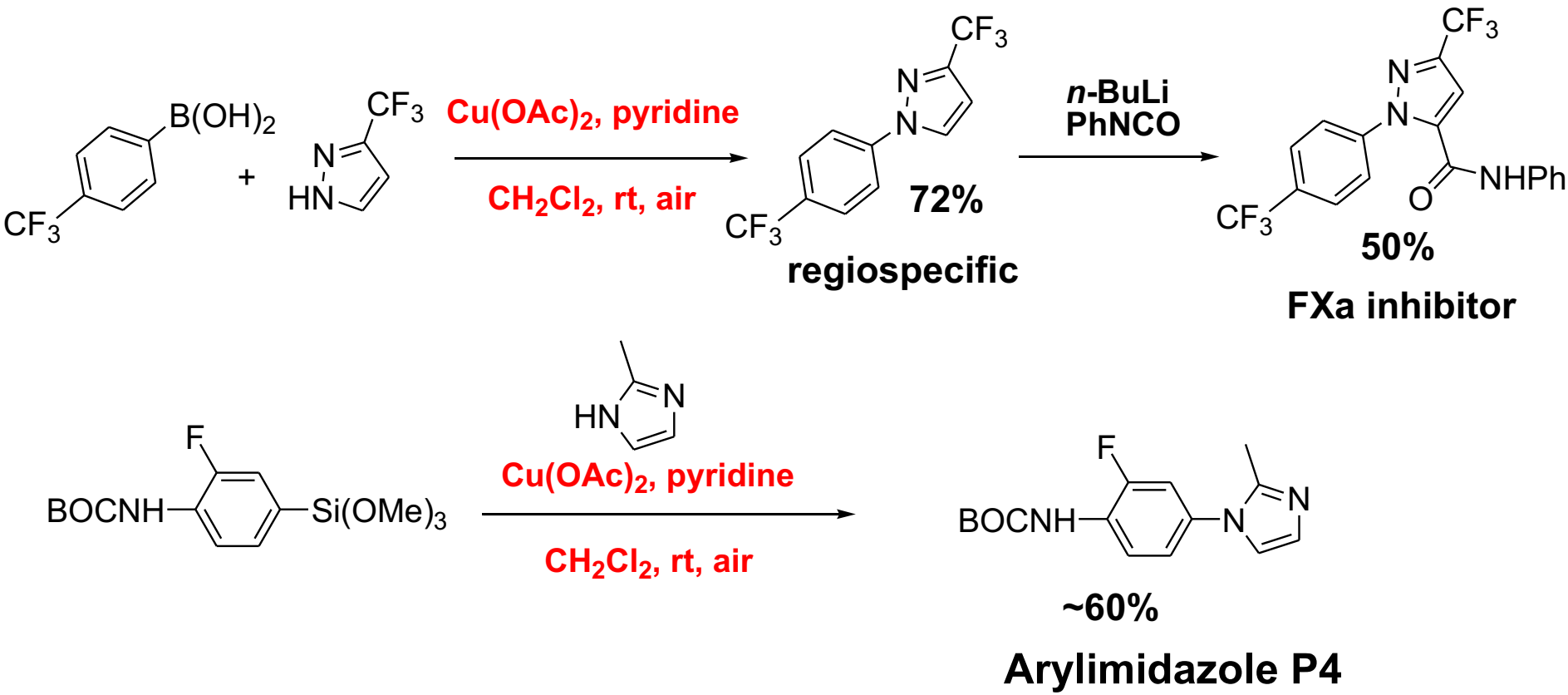
➢ **Unmet medical need for more effective, convenient, and safer oral antithrombotics**



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

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

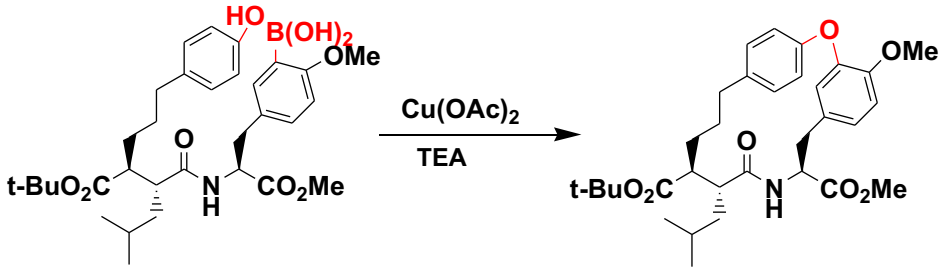
Applications in FXa inhibitor synthesis



Lam, Clark, Li unpublished

Intramolecular O-arylation

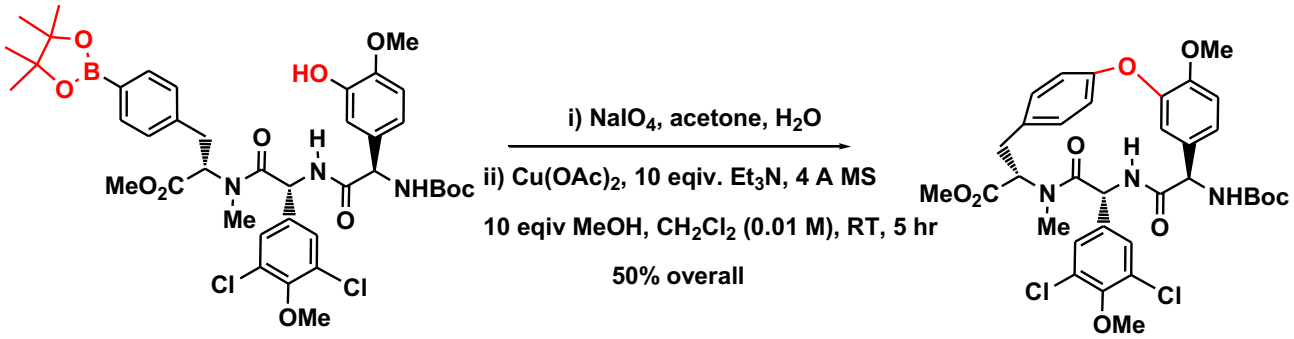
First Intramolecular O-arylation: Synthesis of metalloprotease inhibitors
-other classical methods failed



52%

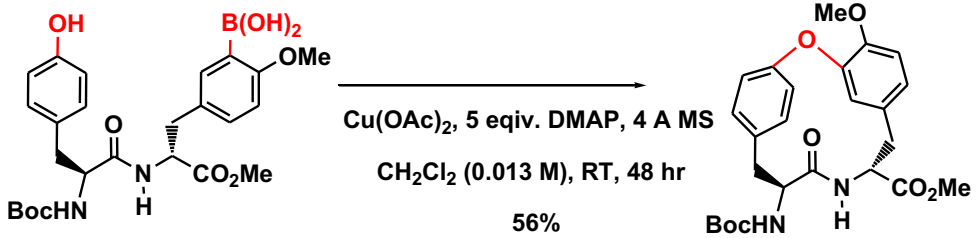
BMS: Decicco, Song, Evans. Org Lett. 1029 (2001)

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



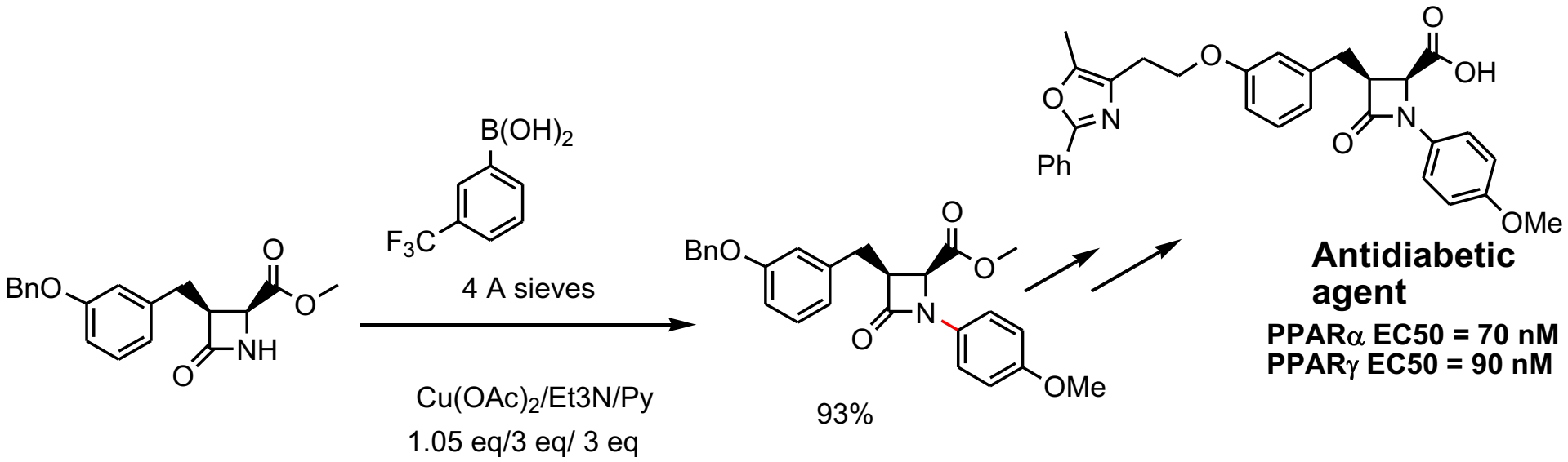
Deng, Jung, Liu, Kuntz, Snapper, Hoveyda. JACS. 9032(2003)

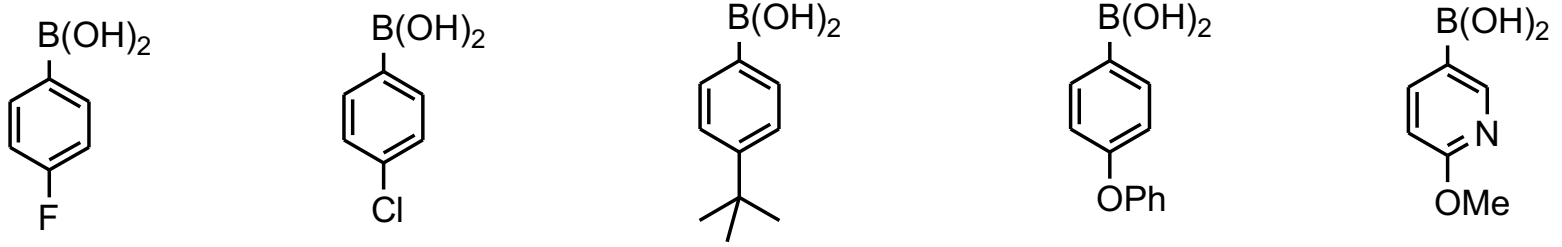
Synthesis of L,L-cycloisodityrosines
-5 eq. DMAP suppresses protio-deboronation



Hitotsuyanagi, Ishikawa, Naito, Takeya. Tet. Lett. 5901(2003)

Application in anti-diabetic agent synthesis





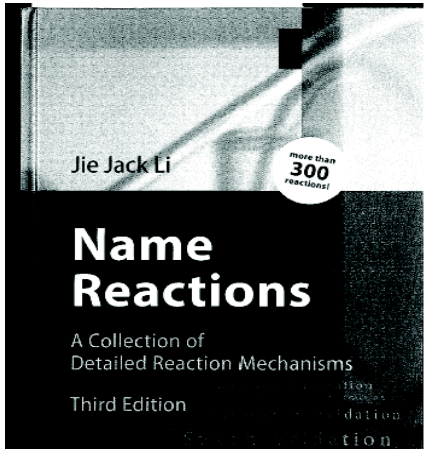
-Remarkable yield with no epimerization.

-α-Carbonyl activating effect is critical, α-acetal lower yield.

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

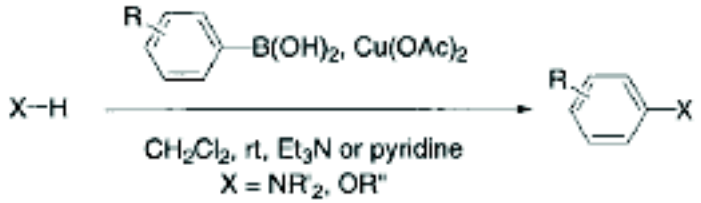


Patrick Lam, Director,
Hopewell Chemistry

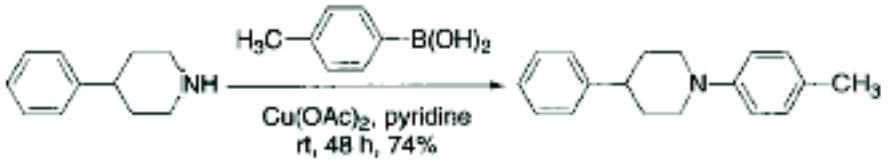


Chan–Lam coupling reaction

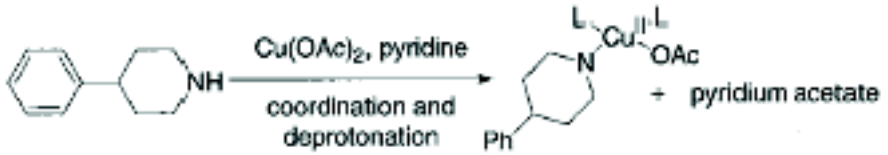
N-Arylation of a wide range of NH substrates by reaction with boronic acid in the presence of cupric acetate and either triethylamine or pyridine at room temperature. The reaction works even for poorly nucleophilic substrates such as arylamide.

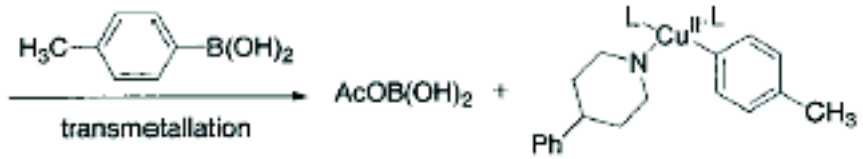


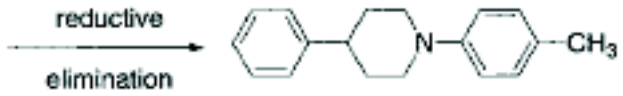
Example 1[1]



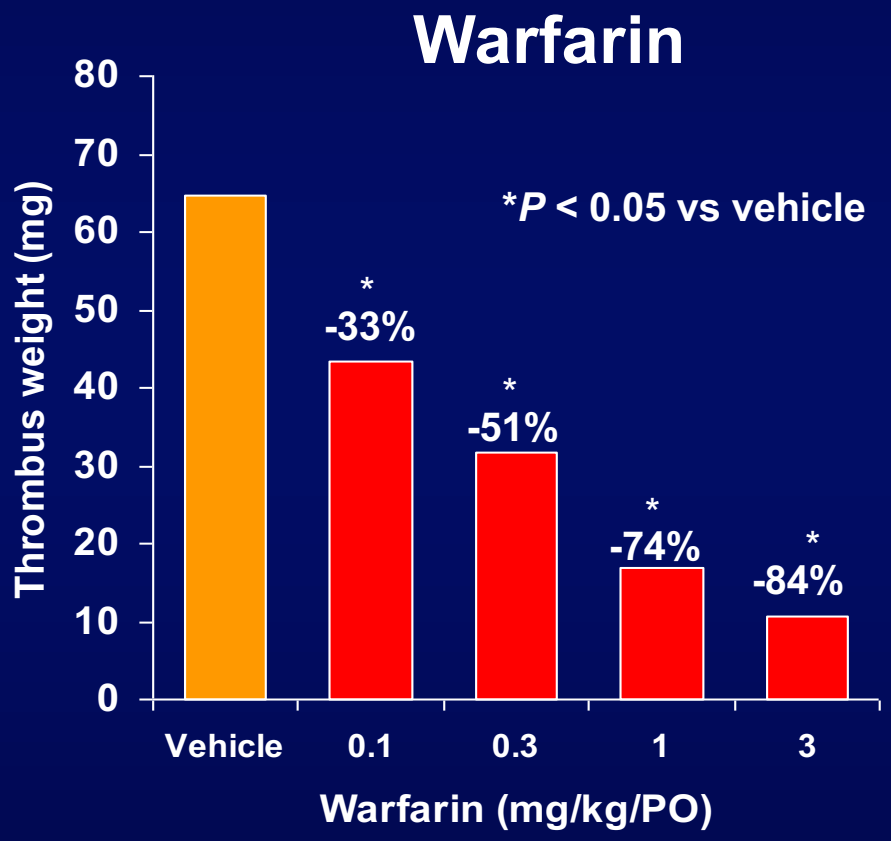
Mechanism:

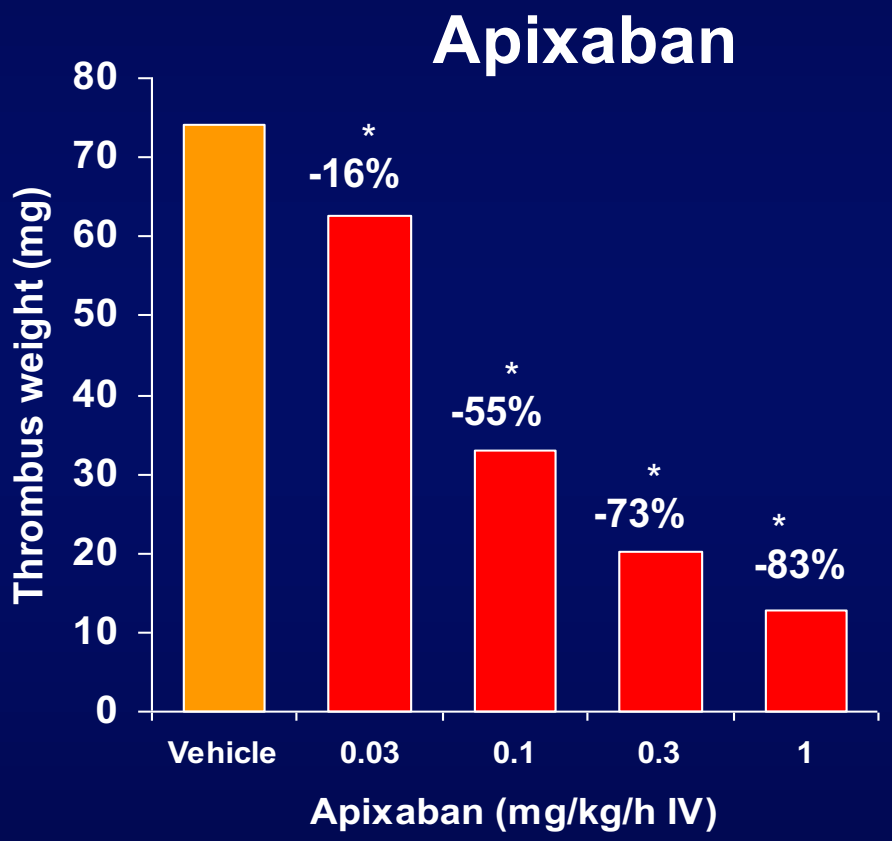






Antithrombotic Effects in DVT Rabbits

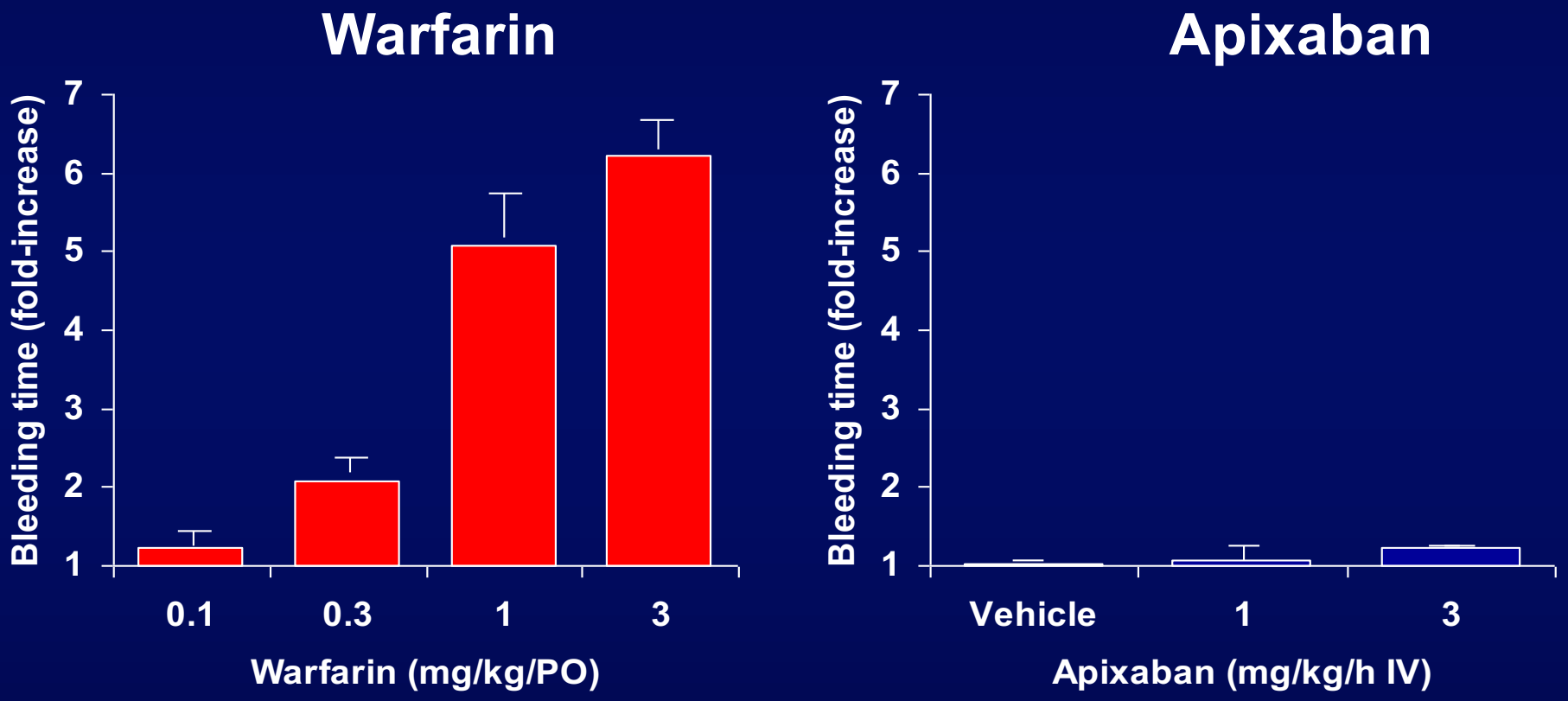




Wong, et al. *J Thromb Haemost.* 2008;6:820-829.

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Bleeding Time Effects in Rabbits

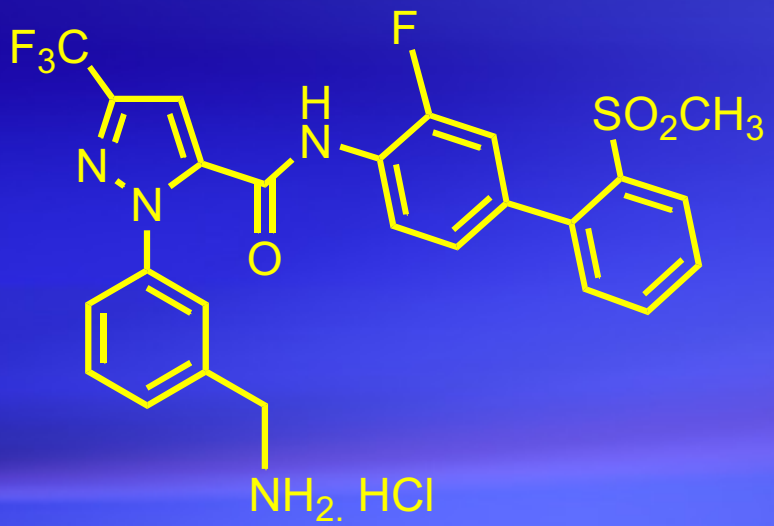


Wong, et al. *J Thromb Haemost.* 2008;6:820-829.

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Apixaban



DPC-423



Razaxaban

1nm

"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

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FXa Acknowledgements

Chemistry

Patrick Lam, Charles Clark, Renhua Li

Bob Galemmo, Brian Wells, Spence Drummond

Don Pinto, Mike Orwat, Gene Amparo,

Shuaige Wang

Mimi Quan, Ming He, Ann Liauw, Chris Ellis

John Fevig, Chris Teleha, Gary Cain, Jung-Hui Sun

Qi Han, Maria Park

Process Chemistry

Luke Rossano

Luigi Anzalone

Rafael Shapiro

Joerg deerberg

Lynnette Oh

Joe Zhou

Ruth Wexler

Paul Anderson

Martin Ogletree

Structural biology

Richard Alexander

Karen Rossi

Biochemistry & Pharmacology

Robert Knabb, Joe Luettgen, Tracy Bozarth

Pancras Wong, Carol Watson, Earl Crain

Alan Rendina, Jeff Bozarth

MAP/Pharmaceutics

Steve Bai

Matt Wright

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

