Translational Success Stories highlight how basic discoveries have led to clinical advances (such as the use of new drugs or diagnostic modalities in patients). This initiative reflects the renewed emphasis of our journal on translational research. It is hoped that these articles will stimulate efforts to translate basic insights into clinical practice.

Translational Success Stories
Development of Direct Thrombin Inhibitors
Michiel Coppens, John W. Eikelboom, David Gustafsson, Jeffrey I. Weitz, Jack Hirsh

Abstract: Anticoagulants are the cornerstone of therapy for conditions associated with arterial and venous thrombosis. Direct thrombin inhibitors (DTIs) are anticoagulants that bind to thrombin and block its enzymatic activity. The bivalent parenteral DTIs hirudin and bivalirudin were based on the observation that the salivary extracts of medicinal leeches prevented blood from clotting. Key events that facilitated the subsequent development of small molecule active site inhibitors, such as argatroban, were the observation that fibrinopeptide A had antithrombotic properties and determination of the crystal structure of thrombin. Hirudin and argatroban have found their niche for the treatment of patients with heparin-induced thrombocytopenia, whereas bivalirudin is approved as an alternative to heparin for patients undergoing percutaneous coronary intervention. The development of orally active direct thrombin inhibitors was challenging because of the need to convert water-soluble, poorly absorbable, active site inhibitors into fat-soluble prodrugs that were then transformed back to the active drug after intestinal absorption. Dabigatran etexilate was the first new oral anticoagulant to be approved for long-term anticoagulant treatment in 6 decades. This Review highlights the development of DTIs as a translational success story; an example in which the combination of scientific ingenuity, structure-based design, and rigorous clinical trials has created a new class of anticoagulants that has improved patient care. (Circ Res. 2012;111:920-929.)

Key Words: thrombin ■ anticoagulant ■ drug development

Direct thrombin inhibitors (DTIs) are anticoagulants that bind directly to thrombin and block its activity. Prior to their development, the injectable anticoagulants in clinical use were heparin and low-molecular-weight heparins (LMWHs). Both are classified as indirect inhibitors because they have no intrinsic activity; instead, they produce their anticoagulant effect by activating antithrombin. The only class of oral anticoagulants that was available at that time was the vitamin K antagonists (VKAs), such as warfarin.

Several key events led to the development of DTIs. The first was the observation in 1884 that salivary secretions of the medicinal leech, Hirudo medicinalis, prevented blood from clotting.1 This finding subsequently led to the development of hirudin, which was initially extracted from leeches and later obtained via rDNA technology.2-5 The second observation, made in 1956 by Bettelheim, was that fibrinopeptide A, a small peptide released from fibrinogen by the action of thrombin, inhibited thrombin activity.6 The third key event in the development of DTIs was the elucidation of the 3-dimensional structure of thrombin, first through molecular modeling and then by x-ray crystallographic analysis of thrombin and the hirudin/thrombin complex in 1989 and 1990, respectively.7,8 These observations and innovations allowed structural chemists to not only design synthetic analogues of hirudin but also to develop small molecules with high affinity and specificity for the active site of thrombin.

The first-generation DTIs were agents that lacked oral absorption and required intravenous or subcutaneous injection. At that time, heparin had been available for 5 decades and LMWHs were established as safe and effective injectable anticoagulants,
but they both had limitations. The anticoagulant effect of heparin is quite variable due to nonspecific protein binding and therefore its dosage must be monitored by laboratory tests. Although LMWHs have a more predictable effect and are administered without the need for coagulation monitoring, the partial thromboplastin time, used to monitor the effects of heparin, is too insensitive for the effects of LMWH. In the setting of percutaneous coronary interventions (PCI), there was a need for a drug with a more predictable effect than heparin that could be easily monitored by a readily available test and that would cause less bleeding than heparin, especially in combination with a glycoprotein (GP) IIb/IIIa inhibitor. Furthermore, like heparin (and later fondaparinux), LMWHs required antithrombin to achieve an anticoagulant effect, thereby providing the DTIs with a potential niche in patients with severe antithrombin deficiency. Finally, heparin, and, to a lesser extent, LMWHs, can cause a serious immune disorder known as heparin-induced thrombocytopenia (HIT), thereby providing the DTIs with a third indication. Another potential advantage of DTIs over heparin is their capacity to inhibit fibrin-bound thrombin as well as free thrombin. Thus, after converting fibrinogen to fibrin, thrombin binds to fibrin, where it can trigger thrombus growth because it is protected from inactivation by antithrombin, even in the presence of heparin.9 By inactivating fibrin-bound thrombin, DTIs might shorten the duration of anticoagulant treatment and be more effective than heparin,9 but this remains unproven.

The second generation of DTIs was orally available. When these agents were developed, there was still no alternative to VKAs. The VKAs had been in use for more than 5 decades and were very effective anticoagulants for long-term administration. However, the variable dose requirements, multiple food-drug and drug-drug interactions, and the need for careful monitoring rendered treatment with VKAs cumbersome, which resulted in both underuse and suboptimal levels of anticoagulation in many patients when they were used. Consequently, there was a large unmet need (as well as a large potential market) for oral anticoagulants that were not handicapped with the limitations of the VKAs. Yet, for several reasons, the development of an oral DTI has been very challenging. First, despite their requirements of therapeutic drug monitoring, VKAs are very effective anticoagulants. As a result, large expensive clinical trials were needed to show either equivalence or clinically worthwhile improvements. Second, development of an oral DTI was technically difficult, requiring the conversion of a small-molecule, water-soluble, poorly absorbable, active site-directed inhibitor into fat-soluble prodrug that is transformed back to the active drug after intestinal absorption. Third, the costs of drug discovery and evaluation are formidable and increasing. As an example, the number of drugs approved per billion US dollars spent on Research and Development has halved roughly every 9 years since 1950, despite technical advances such as x-ray crystallography that have substantially decreased the man-hours needed for 3-dimensional protein design.10 Finally, regulatory requirements are becoming increasingly stringent, so that some promising agents might not be approved even when trial results are favorable.

In this article, we review the development of the DTIs, starting with the medicinal leech and ending with dabigatran etexilate, the first of the oral DTIs to be approved for long-term clinical use (Figure 1). We do not discuss the contentious issue of whether thrombin is the ideal target for new anticoagulants or how it compares with Factor Xa. Resolution of this important issue will require large randomized clinical trials comparing the 2 classes of inhibitors, and until these studies are performed, the answer to this question will remain speculative.

Although chronologically, the story starts with the leech, it is appropriate that we start with the structure and function of the thrombin molecule. We then trace the development of the 2 classes of DTIs, the bivalent inhibitors, of which hirudin is the prototype, and the small-molecule, active-site inhibitors, which include argatroban and melagatran. We then review the science behind the conversion of melagatran to the orally active produg ximelagatran, briefly discussing the reason for its withdrawal from clinical use after very promising phase 3 study results and end with the development of dabigatran etexilate.

Functions and Structure of Thrombin

Functions
Thrombin has procoagulant, anticoagulant, and antifibrinolytic effects, as well as functions that extend beyond hemostasis (Figure 2). In 1905, Morawitz proposed a simple coagulation model that started with prothrombin conversion to thrombin followed by thrombin-mediated conversion of fibrinogen to fibrin.11 We now know that in addition to converting fibrinogen to fibrin monomers, thrombin autocatalytically increases the rate of its own production by activating factors V, VIII, and XI, activates factor XIII, which in turn cross-links and stabilizes the fibrin network, and activates platelets by cleaving the protease-activated receptors (PARs).12 Thrombin modulates hemostasis by binding to its cofactor thrombomodulin, thereby activating the anticoagulant protein C pathway. It also attenuates fibrinolysis through activation of thrombin-activated fibrinolysis inhibitor (TAFI; Figure 2). Finally, thrombin promotes cell proliferation, migration, and vascular permeability and modulates inflammation through activation of PARs, TAFI, and protein C.12

Structure
The 3-dimensional structure of thrombin was first elucidated through molecular modeling and then by x-ray crystallography. Thrombin has 3 functional domains: the active site and 2 positively charged exosites (exosites I and II) to which
substrates and cofactors bind (Figure 3). The active site contains the catalytic triad (serine, histidine, and aspartic acid) that cleaves the appropriate peptide bonds in its substrates, including fibrinogen, clotting factors V, VIII, XI, and XIII, protein C, PARs, and TAFI.12 Exosite I functions as a substrate docking site, thereby enhancing the affinity of the interaction of thrombin with substrates such as fibrinogen or PARs or cofactors, such as thrombomodulin.12 Exosite II binds to heparin, heparan sulfate, and glycoprotein-Ib/Ho on platelets.

Our knowledge of the structure and function of thrombin was greatly advanced when the x-ray crystallographic structure of thrombin bound to D-Phe-Pro-Arg chloromethylketone (PPACK), a peptide that binds irreversibly to the active site of thrombin, was described by Bode and colleagues in 1989 (Figure 2).7 They demonstrated that the active site of thrombin is hidden within a deep cleft consisting of a more polar base and hydrophobic rims. This cleft endows thrombin with specificity for its substrates because the substrate must fit within the cleft so that the appropriate bond is cleaved.7 In 1990, x-ray crystallography also unraveled the details of the bivalent interaction between recombinant hirudin and thrombin.8 The amino (N)-terminus of hirudin partly obstructs the active site of thrombin, whereas the longer carboxy (C)-terminus tail of hirudin binds exosite I, a narrow canyon adjacent to the active site.8

Fibrinopeptide A Analogs Serve as Competitive Inhibitors of Thrombin

To convert fibrinogen to fibrin, thrombin releases fibrinopeptide A (FPA) and B. In 1956, Bettelheim showed that FPA...
Hirudin

In 1884, Haycraft reported that the medicinal leech Hirudo medicinalis produces a substance that had anticoagulant properties. An anticoagulant extract was isolated from these leeches in 1903 for which the name hirudin was suggested. At that time, the structure of the anticoagulant was unknown, but it was presumed to be a protein. In 1956, a group led by Markwardt demonstrated that hirudin isolated from the salivary glands of medicinal leeches inhibited thrombin. In the following years, the isolation and purification of hirudin were optimized and it was found to consist of 65 amino acids.

Studies with hirudin in animals and humans were performed in the early 1980s, but its clinical evaluation was hampered because of the tedious extraction procedures and the fact that medicinal leeches had been placed on a list of endangered species. This problem was resolved when recombinant hirudin was developed in 1986. Recombinant hirudin differs from native hirudin in that the Tyr residue at position 63 is not sulfated. Although this difference marginally reduces its affinity for thrombin, recombinant hirudin remains a potent and highly specific inhibitor of thrombin.

Clinical Trials With Recombinant Hirudin

There are 2 forms of recombinant hirudin: lepirudin and desirudin. The 2 forms are structurally identical except for their N-terminus sequences, which are Leu1-Tyr2 in lepirudin and Val1-Val2 in desirudin.

Recombinant hirudins have been evaluated in randomized, controlled trials for the prevention and treatment of venous thrombosis and for the treatment of patients with acute coronary syndromes. Desirudin was reported to be more effective than LMWH (enoxaparin) for prevention of venous thromboembolism (VTE) in patients undergoing hip replacement surgery. A VTE treatment study comparing desirudin with usual care was small and produced inconclusive results. Lepirudin and desirudin were compared with heparin in patients with acute coronary syndromes. Desirudin was associated with an increased risk of bleeding.

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When compared with historic controls, lepirudin showed promising results in patients with HIT and associated arterial and/or venous thrombosis, reducing the risk of death and new thromboembolic events.\textsuperscript{27} Lepirudin has also shown promise when evaluated as an alternative to hirudin in patients with a history of HIT undergoing cardiopulmonary bypass surgery.\textsuperscript{28}

Recombinant hirudin stimulates antibody development in up to 40\% of patients. Although most of these antibodies appear to be of no clinical relevance, they may prolong the half-life of hirudin, which can lead to drug accumulation. Anaphylactic reactions have been reported on re-exposure to recombinant hirudin in patients with antibodies.\textsuperscript{29} The increased risk of bleeding heparin, concerns about immunogenicity, and high cost have limited the use of hirudin. Lepirudin is approved for the treatment of patients with suspected or proven HIT and those deemed to be at risk of developing HIT, whereas desirudin is approved in the United States, Europe, and Australia for the prevention of VTE after hip replacement (Table).

Other anticoagulants, including danaparoid, fondaparinux, argatroban, and bivalirudin, are also used to treat patients with HIT. Danaparoid is a mixture of heparin, chondroitin and dermatan sulfate, and fondaparinux; all are indirect anticoagulants that require antithrombin as a cofactor.\textsuperscript{29} Danaparoid is licensed for treatment of HIT in most countries but is not available in the United States. Fondaparinux is not approved for HIT treatment but is nevertheless widely used for this indication, supported by evidence in the literature for its efficacy.\textsuperscript{30,31} Argatroban has been evaluated in HIT in nonrandomized studies (see below), and bivalirudin has been used in HIT patients undergoing PCI or coronary bypass surgery. Desirudin is rarely used for prevention of VTE after hip replacement surgery because of substantial competition from other drugs: LMWHs, fondaparinux, dabigatran etexilate, an oral DTI (see below), and rivaroxaban and apixaban, which are oral factor Xa inhibitors.\textsuperscript{29}

**Hirugen and Bivalirudin (Hirulog)**

In the late 1980s, a group led by Maraganore embarked on a program to develop a synthetic hirudin. They started by synthesizing a number of peptides based on the structure of.
Development of Direct Thrombin Inhibitors

Small-Molecule, Active Site–Directed DTIs

Starting first with argatroban, a parenteral DTI that targets the active site of thrombin, attention then focused on oral DTIs. The first of the oral agents was ximelagatran, which was briefly licensed for limited indications. The most recent oral DTI is dabigatran etexilate.

Argatroban

Building on the Phe-Val-Arg sequence discovered in the studies by Bettelheim and Blombäck,6,14 in 1972, a group led by Okamoto in collaboration with Mitsubishi Chemical Industries in Japan embarked on a program to develop a DTI.48 They synthesized and tested several hundreds of candidate compounds from which argatroban emerged in 1981 as the most potent inhibitor.49 Unexpected at that time, changes in the stereostructure of the hydrophobic portion of argatroban resulted in large differences in thrombin inhibitory potency.49 This finding would later be explained by x-ray crystallographic analysis of the thrombin-argatroban complex, which revealed the interactions between the hydrophobic portion of argatroban and the hydrophobic pockets adjacent to the active site of thrombin.50 The interaction of argatroban is similar to that of melagatran and dabigatran, drugs that would be developed later (see below).

Clinical Trials With Argatroban

Argatroban’s main indications are the prevention and treatment of thrombosis in patients with HIT and the treatment of patients with or at risk of HIT undergoing PCI (Table). Approval for these indications was received on the basis of 2 observational studies involving a combined total of more than 500 patients with HIT.51,52 In Japan only, argatroban is also licensed for treatment of ischemic complications in patients with chronic peripheral arterial occlusions and for treatment of patients with ischemic stroke.53,54 Argatroban has also been evaluated in several small, randomized, controlled trials in patients with acute coronary syndromes, but results were inconclusive.55–57

Oral DTIs

The development of an orally absorbable thrombin inhibitor presented a number of challenges. To be intestinally absorbed, a compound requires 2 essential characteristics. First, the drug must have a molecular weight below 500 Da so as to be small enough to pass through the intestinal wall.58 This size requirement disqualifies recombinant hirudin and bivalirudin (with molecular masses of 6.9 and 2.2 kDa, respectively) but qualifies small molecules targeting the active site. The second requirement for oral absorption is lipophilicity.58 Such a requirement posed a particular challenge for DTIs because the active site pocket of thrombin is hydrophilic.7 Thus, to be orally available, DTIs had to be sufficiently lipophilic to be absorbed by the intestine but required hydrophilic groups to bind to thrombin. The problem was solved by adding lipophilic end-groups so that the compound remained stable in the gut but was metabolically converted into the active drug once it was absorbed into the bloodstream. More than 7000 patents for oral thrombin inhibitors can be found through Google Patents (www.google.com/patents), but, thus far, only dabigatran etexilate has been registered as an oral DTI for long-term clinical use. Before dabigatran etexilate was approved, ximelagatran was evaluated in a large

Bivalirudin has been approved for patients with acute coronary syndromes, for those undergoing PCI, and for patients undergoing PCI who have or are at risk of HIT (Table). For these indications, bivalirudin’s main competitors are heparin in combination with a GP IIb/IIIa inhibitor, heparin alone, or LMWH.
phase 3 clinical trial program. The creative pioneering work with ximelagatran paved the way for the development of other orally absorbed direct thrombin and factor Xa inhibitors.

**Melagatran and Ximelagatran**  
In the mid 1980s, a research team at AstraZeneca in Sweden embarked on a project to develop an orally active thrombin inhibitor. The starting point was a pentapeptide based on the structures of fibrinogen and FPA that bind to the active site of thrombin. Appreciating the need for a small-molecule inhibitor, development shifted to a dipeptide. In an iterative process, numerous compounds were synthesized and tested in vitro and in animal models. X-ray crystallography and computerized modeling were used to guide the selection process, and in 1993, a benzamidine-based compound named melagatran was selected for evaluation in humans. In animal models, the dose-response curve for melagatran was less steep than of warfarin, leading the inventors to speculate that the DTI would have a more favorable therapeutic index. When tested in humans, the oral bioavailability of melagatran was only about 3% to 7%, plasma concentrations were variable and unpredictable, and there was a pronounced food interaction. Further studies identified 3 charged groups as the cause of the limited gastrointestinal absorption. To overcome the poor oral bioavailability, efforts were directed to design a lipophilic prodrug that would be intestinally stable, could pass the intestinal wall, and, once absorbed, be metabolized to melagatran. Inspired by a preliminary presentation of the design of a newly developed double prodrug for a glycoprotein IIb/IIIa inhibitor, a prodrug with 2 lipophilic groups, which was transformed into melagatran after absorption, was developed. This prodrug was named ximelagatran. Crucial to this discovery process was the availability of an in vitro model, consisting of a monolayer of epithelial cells from a colon cancer cell line (Caco-2), which was used to test gastrointestinal permeability. Ximelagatran passed through this monolayer 80 times faster than melagatran, and the prodrug was carried forward to studies in humans.

**Clinical Trials With Melagatran**

In an extensive clinical research program, melagatran was investigated for the following indications: VTE prevention after orthopedic surgery, initial and long-term treatment of symptomatic VTE, stroke prevention in patients with atrial fibrillation, and secondary prevention of major cardiovascular events after myocardial infarction. Unfortunately, about 6% of patients treated with ximelagatran for VTE treatment and stroke prevention in atrial fibrillation developed elevations in liver transaminases. Even though most of these elevations were asymptomatic and transient, the mechanism was poorly understood and transaminase elevations could even occur after the drug was stopped. Ximelagatran was not granted approval in the United States. In Europe, it was briefly licensed for VTE prevention in orthopedic surgery until the company decided to withdraw ximelagatran due to these liver problems. A case-control study of patients who had been treated with ximelagatran demonstrated that the hepatic adverse effects were associated with 2 specific MHC alleles (DRB1*07 and DQA1*02), suggesting that they may be allergic in nature. Nonetheless, the favorable efficacy and limited bleeding risk of ximelagatran represented an important step forward in drug development because it supported the concept that small-molecule, orally active DTIs or direct factor Xa inhibitors could be used in fixed doses without coagulation monitoring.

**Dabigatran Eteixlate**

To develop dabigatran etexilate, scientists at Boehringer Ingelheim utilized 2 key concepts. The first, as shown with melagatran, was that benzamidine-based compounds could form the basis of oral DTIs. The second was that a hydrophilic compound can be converted into a lipophilic prodrug, which is then transformed back to the active drug after intestinal absorption. The x-ray crystal structure of thrombin in complex with the peptide-like, benzamidine-based inhibitor NAPAP was used as the starting point for the development of dabigatran. Through an iterative process involving advanced molecular synthesis, x-ray crystallographic fitting, in vitro testing, and animal models, the most promising compound was selected for further evaluation. Building on the same double prodrug design of the glycoprotein IIb/IIIa inhibitor that inspired the development of ximelagatran, a prodrug was developed through esterification of the hydrophilic benzamidine-based inhibitor, thereby converting it to a more lipophilic prodrug, BIBR 1048, which was later named dabigatran etexilate. Once absorbed, esterases in the liver and plasma metabolize the prodrug into active dabigatran. Dabigatran etexilate, which was combined with tartaric acid to improve intestinal absorption, has an oral bioavailability of 6.5% in healthy human volunteers.

**Clinical Trials With Dabigatran Eteixlate**

Dabigatran etexilate has completed testing in an extensive phase 3 clinical trial program for VTE prevention in patients undergoing hip or knee replacement, for treatment of symptomatic VTE, and for stroke prevention in patients with atrial fibrillation. In the trials for VTE prevention, dabigatran etexilate was associated with similar efficacy and safety compared with warfarin. For VTE treatment, dabigatran etexilate was noninferior to warfarin. For stroke prevention in patients with atrial fibrillation, 2 doses of dabigatran etexilate were compared with warfarin in more than 18,000 patients. Patients receiving the higher dose of dabigatran had a lower risk of stroke and a similar risk of bleeding compared with warfarin, and patients receiving the lower dose had a similar risk of stroke and a lower risk of bleeding. Like other small-molecule inhibitors, dabigatran etexilate was given in fixed doses without routine coagulation monitoring or dose adjustments.

Dabigatran has been approved for VTE prevention in orthopedic patients and for stroke prevention in patients with atrial fibrillation (Table). For the latter indication, dabigatran etexilate was the first alternative to VKAs for long-term anticoagulant treatment after more than 6 decades. Although the first of the new oral anticoagulants to be licensed for the atrial fibrillation, dabigatran etexilate is now facing competition from the oral factor Xa inhibitors. Rivaroxaban is also licensed for stroke prevention in atrial fibrillation, and apixaban is likely to soon follow. Edoxaban, a third oral factor Xa inhibitor, is currently still under investigation in a phase 3 trial.
Conclusion

DTIs represent a new class of anticoagulant drugs. The parenteral DTIs, lepirudin and argatroban, have found their niche in the treatment of patients with HIT, whereas bivalirudin is a widely used alternative to heparin in patients with acute coronary syndromes and in those undergoing PCI. Although the development of oral DTIs was more challenging, the benefits to patients and rewards to the developers are likely to be greater because they serve a greater clinical need. The discovery and development of these new anticoagulants is a translational success story, combining modern technologies with scientific ingenuity and rigorous clinical trial design.

Disclosures

M.C. has received lecturing fees from Bayer and a research grant from Boehringer-Ingelheim. J.W.E. has received honoraria and research support from companies that market new oral anticoagulants including Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Pfizer, and Portola. D.G. is employed by AstraZeneca, which developed and marketed ximelagatran until its withdrawal in 2006. J.I.W. has served as a consultant and has received honoraria from Boehringer-Ingelheim, Bristol-Myers Squibb, Pfizer, Bayer, Janssen Pharmaceuticals, Daiichi Sankyo, and Takeda.

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Circ Res. 2012;111:920-929
doi: 10.1161/CIRCRESAHA.112.264903
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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