



## CASE TWO

# Integrilin®

## Summary

Integrilin® (eptifibatide) is an antiplatelet drug developed by COR Therapeutics from the stage of basic research on snake venom to an FDA-approved drug, which has been used worldwide by millions of patients with cardiovascular disease since its approval in 1998. COR Therapeutics was ultimately acquired by Millennium Pharmaceuticals for \$2 billion in 2002. Some key lessons that can be learned from Integrilin® include insights into how to identify [unmet clinical needs](#); the advantages of developing a [small molecule aimed at the validated target of a biologic](#); the choice faced by academic founders between [staying in academia](#), where only part of their time could be dedicated to the new venture, and [leaving to become a full-time executive](#); the importance of [partnerships](#) during the drug development and regulatory process; and the crucial role that a successful [reimbursement strategy](#) can play in marketing a novel drug.

### *Addressing an unmet need: reducing thrombus formation by inhibiting a new target*

Developed in the [1970s](#), percutaneous coronary interventions (PCI) revolutionized the management of patients with coronary artery disease, becoming an important life-saving procedure performed on over 3 million patients per year worldwide, and representing a \$10 billion market in the United States.<sup>1,2</sup> Despite good clinical results, this procedure led to thrombotic complications due to vascular injury caused by the treatment devices, increasing the need for new anti-thrombotic therapies.

---

### DISCUSSION POINTS

- [Recognizing Unmet Needs](#)
  - [Target Product Profile: Biologics vs. Small Molecules](#)
  - [Team Formation: Leaving Academia](#)
  - [Partnerships](#)
  - [Reimbursement](#)
- 

In the 1980s, the targets of clinically available drugs were limited to individual pathways of platelet activation. For example, aspirin blocks thromboxane A<sub>2</sub> synthesis, but

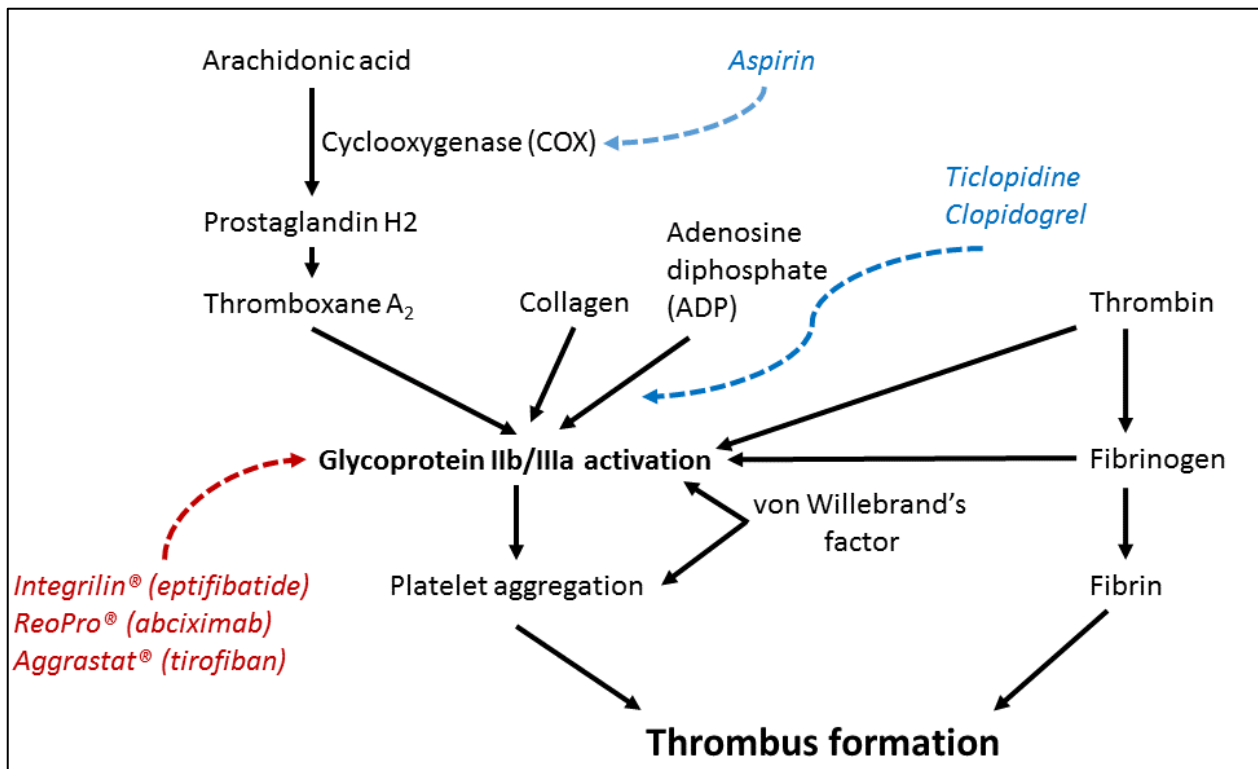
leaves thrombin-induced platelet aggregation unaffected. It quickly became clear that more significant inhibition of platelet aggregation was needed to reduce the formation of coronary thrombi.<sup>3</sup>

Based on studies of a rare autosomal recessive bleeding disorder (Glanzmann thrombasthenia) characterized by deficient or dysfunctional glycoprotein (GP) IIb/IIIa complexes, scientists at the State University of New York (SUNY) developed a monoclonal antibody 7E3 (abciximab) targeted against GPIIb/IIIa,<sup>4</sup> which, when activated, undergoes a conformational change enabling it to bind fibrinogen, von Willebrand factor, fibronectin, and vitronectin. When GPIIb/IIIa binds to

fibrinogen and von Willebrand factor, GPIIb/IIIa molecules on adjacent platelets undergo cross-linking, leading to platelet aggregation and thrombus formation (Figure 1). 7E3 showed promising results, and the technology was licensed to CENTOCOR in [1986](#), eventually becoming the FDA-approved biologic ReoPro® (abciximab).

### Identifying the opportunity and developing a clear target product profile

At that time, it was not totally clear that the monoclonal antibody therapy against GPIIb/IIIa (abciximab) would succeed as an antiplatelet treatment, but the biology was very compelling. At the University of California, San Francisco (UCSF), two cardiologists, [Shaun Coughlin](#) and [Lewis T.](#)



**Figure 1. Thrombus formation pathway and mechanism of glycoprotein IIb/IIIa inhibitors compared to other drugs used to inhibit thrombus formation**

[“Rusty” Williams](#), knew that abrupt closure after PCI stent placement was a major problem and that developing a small peptide would have advantages over an antibody-based therapy against GPIIb/IIIa such as abciximab. A small peptide had the potential to be fast-acting and reversible, which was desirable in the context of PCI. Coughlin and Williams’ research was then focused towards the development of an inhibitor of the platelet-derived growth factor (PDGF) receptor, another hot target in cardiovascular research, aiming to reduce the rate of restenosis following balloon angioplasty. [David Phillips](#), then a faculty member at the Gladstone Institute, was considered the world’s expert on GPIIb/IIIa. Shaun, Rusty, and David met after one of David’s lectures and started a collaboration, searching for new compounds that could reduce the risks of PCI (including restenosis after stent or balloon angioplasty) and also be adequate for other indications, such as unstable angina.

### ***Founding COR***

In [1988](#), a partner at a venture capital firm, [Lee Douglas](#), who had previously been involved in starting a successful protein design company, approached faculty members at UCSF with the goal of funding new technologies in neuroimmunology. However, after meeting with Coughlin, Williams, and Phillips, he became very interested in cardiovascular research, and COR Therapeutics was founded shortly thereafter. Coughlin, Williams, and Phillips were the scientific founders, and Lee Douglas

and [Bob Swift](#), a proven company builder and recognized operations expert, were tasked with developing the business (Table 1).

**Table 1. Backgrounds of the COR Therapeutics co-founders when the company was founded.**

<p><b>R. Lee Douglas, MBA</b>  MBA from Harvard University  Former partner at Robertson, Stephens &amp; Co., (venture capital firm)  Co-founder and CEO of COR Therapeutics</p>
<p><b>David R. Phillips, PhD</b>  PhD from University of Southern California  Associate Professor of Pathology and Senior Scientist, Gladstone Institute  Co-founder and CSO of COR Therapeutics</p>
<p><b>Shaun R. Coughlin, MD, PhD</b>  PhD from Massachusetts Institute of Technology  MD from Harvard Medical School  Assistant Professor of Medicine, UCSF  Co-founder of COR Therapeutics</p>
<p><b>Lewis T. “Rusty” Williams, MD, PhD</b>  MD and PhD from Duke University  Professor of Medicine, UCSF  Co-founder of COR Therapeutics</p>
<p><b>Robert L. Swift, PhD</b>  Head of Clinical Research and Biostatistics, Genentech  Co-founder of COR Therapeutics</p>

PhD - Doctor of Philosophy; CEO - Chief Executive Officer; CSO- Chief Scientific Officer; MBA -Master of Business Administration

When COR was founded, Phillips left academia and Douglas left his partnership at the venture company firm Robertson, Stephens & Co. in order to take on the full-time roles of Chief Scientific Officer (CSO) and Chief Executive Officer (CEO), respectively. Phillips also convinced Israel “Izzy” Charo, MD, PhD, then an assistant professor at UCSF who worked in his lab, to leave academia and join COR as a principal scientist. They played a critical role in

building the company, and in particular, Phillips and Charo were able to leverage their expertise on GPIIb/IIIa to shape the focus of COR.

COR had initially two programs: one focused on the development of PDGF receptor inhibitors and the other focused on developing GPIIb/IIIa inhibitors. Their initial goal was to use crystallography to design the inhibitors. Looking back, Charo now describes it as being a very ambitious idea, considering the large protein-protein interface and the fact that almost none of it had been crystalized.

As the CEO of COR, one of Douglas' first decisions was to hire two chemists who were well recognized as "drug hunters": David Wolf, PhD and Robert Scarborough, PhD. Scarborough directed the attention of the scientific team to two interesting papers published in 1987 and 1988, authored by scientists at Temple University and at Merck Sharp and Dohme Research Laboratories, that described anti-platelet aggregation proteins isolated from snake venoms.<sup>5,6</sup> He then suggested that COR should go in the same direction and "search for its own snake". The academic founders initially resisted Scarborough's idea, arguing that it was not compelling science, but eventually they began to buy snake venoms from Sigma to pursue this project.

After screening many snake venoms, the COR team scientists isolated barbourin, a protein with a very specific affinity for GPIIb/IIIa.<sup>7</sup> Barbourin provided the template

for the development of eptifibatide, a small nonimmunogenic peptide with a high affinity for GPIIb/IIIa and rapid clearance from circulation.

## Partnerships and trials

In [1990](#), the safety of eptifibatide was successfully established in normal healthy volunteers in a phase I trial. In the following year, COR entered into a four-year partnership with Eli Lilly, in which Eli Lilly provided funding for COR in exchange for the rights to market a set of next-generation drugs targeting fibrinogen receptors that were under development at that time. However, Eli Lilly did not acquire the rights to eptifibatide as part of this deal due to disagreements about its valuation. This deal gave COR the funding to further pursue the development of eptifibatide as part of its larger portfolio.

In the 1990s, multiple GPIIb/IIIa inhibitors were moving towards the market, meaning that COR was not developing eptifibatide in isolation. In [1992](#), Eli Lilly signed an agreement with Centocor for the development of abciximab (ReoPro®), a biologic inhibitor of the GPIIb/IIIa receptor. ReoPro® received FDA approval in [1994](#), making it the first FDA-approved drug in its class. By the time ReoPro® was approved, eptifibatide had already gone through two phase II trials to establish the pharmacodynamics and the preliminary safety profile of eptifibatide: Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT) and IMPACT-Hi/Low.

The IMPACT-II trial, conducted from November [1993](#) to November [1994](#), was a phase III clinical trial that investigated the efficacy of eptifibatide in treating patients who underwent elective, urgent, or emergency coronary interventions. Two 24-hour infusion dosages (0.5 and 0.75  $\mu\text{g}/\text{kg}$ ) of eptifibatide were tested following a bolus injection of 135  $\mu\text{g}/\text{kg}$ . At 24 hours, a highly significant relative reduction (30%–35%) was observed for the composite end point (death, myocardial infarction, coronary artery bypass grafting, repeat urgent or emergent coronary intervention, or stent placement for abrupt closure) with both dosages of eptifibatide compared to placebo.<sup>8</sup> However, the results regarding the primary composite endpoint at 30 days were puzzling. The difference among the groups was less evident and depending on the method used for the data analysis, the statistical significance at the level of  $p < 0.05$  was not achieved.<sup>9,10</sup> These results suggested that the efficacy of eptifibatide was largely due to the initial bolus injection, rather than the continuous infusion. These findings also suggested that neither of the infusion regimens adequately inhibited platelet function. When COR announced the trial results, its shares sank 45%.<sup>11</sup> Phillips then discovered that the effects of eptifibatide were overestimated in the ex vivo pharmacodynamic studies due to the use of sodium citrate in the blood samples.<sup>12</sup> It is currently estimated that the doses used in the IMPACT-II trial achieved less than 50% of maximal platelet blockade.<sup>10</sup>

In [1995](#), Schering-Plough Ltd. and COR entered into an agreement to co-promote the drug in the U.S., while Schering-Plough would market Integrilin® in Europe and several non-European countries on a royalty-bearing basis. This agreement provided COR with funding and expertise to design later-stage clinical trials.

From November 1995 to January [1997](#), a second phase III clinical trial of eptifibatide, known as the PURSUIT trial, was conducted using an increased dose of eptifibatide (180  $\mu\text{g}/\text{kg}$  bolus followed by 2.0  $\mu\text{g}/\text{kg}$  infusion). Treatment with eptifibatide was found to lead to a statistically significant decrease in the incidence of death or nonfatal myocardial infarction ( $p = .04$ ).<sup>9</sup>

While some tension existed between the Schering team and the COR team regarding trial design, the trials co-sponsored by Schering proved Integrilin's clinical efficacy and contained data on resource utilization that would ultimately prove crucial in marketing Integrilin® by allowing COR and Schering to make a strong argument to hospitals on the basis of cost-effectiveness.

## **FDA approval**

Integrilin® received FDA approval in May [1998](#). By this time, ReoPro® had been approved for nearly four years. Moreover, another non-biologic GPIIb/IIIa inhibitor, Aggrastat® (tirofiban) was approved by the FDA in the same month Integrilin® was approved, meaning that Integrilin® was entering a relatively crowded market. COR

faced the challenge of differentiating Integrilin® from its competitors and carving out a market share. COR adopted three strategies for overcoming this challenge: (1) competing with ReoPro® by stressing Integrilin®’s advantages as a non-biologic compound; (2) continuing to conduct clinical research on Integrilin® and using cost-effectiveness data from their clinical research and other studies to gain market share; and (3) partnering with Schering-Plough to market Integrilin® and conduct research into its cost-effectiveness.

## **Acquisition by Millennium Pharmaceuticals**

In the third quarter of [2001](#), sales of Integrilin® had reached \$55 million. Co-founder Dr. Shaun Coughlin stated that the profitability of COR at this point made them a “target for acquisition.” In December [2001](#), COR was acquired by Millennium Pharmaceuticals for \$2 billion. As Coughlin recalls, a compelling aspect of Millennium’s offer was that they were willing to provide resources for COR’s other programs (such as a tyrosine kinase receptor program), although these programs were ultimately spun out into the portfolio of Portola Pharmaceuticals.

By [2007](#), Integrilin® was used to treat approximately one million patients per year, with sales of \$320 million. Subsequently, Plavix® (clopidogrel) emerged as a compelling drug for many of the indications of Integrilin®, and Integrilin®’s sales dropped to \$186 million in [2013](#). As of

June [2015](#), Integrilin® is off patent, and is expected to be a “generic blockbuster”.<sup>13</sup>

## *Discussion*

### *Recognizing Unmet Needs*

Integrilin® was developed to address clinical needs that emerged after the widespread implementation of percutaneous coronary interventions (PCI), a novel procedure. The first step in the process of translational research is to identify an unmet medical need, which refers to a situation where no adequate tools are available for the diagnosis, treatment, or prevention of a given condition, or if a new product would be dramatically more effective than existing options.

COR’s founding team included two physician-scientists who were able to identify the clinical need for a more potent antiplatelet drug that emerged after the widespread implementation of PCI. This underscores the point that newly developed procedures may create an increased need for new pharmaceutical interventions. The COR founders were also able to draw upon basic scientific principles to recognize that a small-molecule drug would be more advantageous in that clinical context because it would be cleared faster from the bloodstream.

Multidisciplinary teams are highly desirable in translational research, and

physician-scientists frequently play an important role in developing translational products.<sup>14,15</sup> Collaborations between clinicians and basic researchers benefit the translational process. The advancement of patient care is generally driven by the recognition of unmet needs that are addressed by creative multidisciplinary teams through the development of new medical technologies.

### **Biologics versus Small Molecules**

One of the major advantages of Integrilin® over ReoPro® was that Integrilin® is a small-molecule drug, whereas ReoPro®, a monoclonal antibody, is a biologic compound. Biologics are compounds produced by living organisms, such as microorganisms and plant or animal cells. Biologics tend to be much much larger than drugs (for instance, the molecular weight of ReoPro® is over 47 kDa, compared to 0.832 kDa for Integrilin®) and require special considerations in the production process and with regard to intellectual property (IP) protection. From a clinical point of view, one of the major advantages of Integrilin® was that it is short-lived and reversible. In the words of co-founder Dr. Shaun Coughlin, “the reversibility of Integrilin® was appealing in the setting of PCI and unstable angina...as compared to an antibody that’s going to be around for a couple of weeks.” Moreover, due to the more streamlined process involved in producing small-molecule drugs, the cost per dose of

Integrilin® was much lower than for ReoPro®.

Biologics are often heterogeneous in structure, immunogenic, and relatively sensitive to storage conditions. One of the major challenges in developing a biologic is that small changes in the manufacturing process can result in significant changes to the final product, due to the inherent variability of natural systems. Moreover, IP protection for biologics applies to the manufacturing process, not the final product, creating challenges for drug developers. Nonetheless, biologics are compelling products for drug development programs because they can exert powerful therapeutic effects by modulating protein-protein interactions that are difficult to target with small molecules. Also, biologics that enter clinical testing are approved more than three times as often as small-molecule drugs, and they are playing an increasingly large role in the overall pharmaceutical market.

The development of small-molecule drugs with the power of biologics has been described as the “holy grail of drug development.”<sup>16</sup> One of the reasons for the success of Integrilin® was that it achieved this goal, as a small molecule with activity at the validated target of the biologic ReoPro®. While this may not always be feasible for all drug development programs, the case of Integrilin® provides a vivid example of the relative advantages and disadvantages of biologics and small-molecule drugs.

### **Team Formation: Leaving Academia**

When forming a new company, academic innovators may face a choice between leaving academia to pursue the development of their company full-time and remaining in academia and contributing to the growth of the company on a more part-time, advisory basis. Since two academics did leave academia to serve as the principal scientist and CSO of COR, this case study provides a valuable perspective on the ramifications of this decision.

Building a pharmaceutical company is very different from developing a research lab in academia. A much greater emphasis is placed on developing a marketable product than on basic research, and the extensive process of drug development and regulatory approval requires working with a range of partners who can provide the necessary expertise and manpower.

However, in some cases, leaving academia to head a start-up can allow an academic innovator to have a profound impact on the trajectory of the company and its products. For example, the COR co-founder Dr. Shaun Coughlin, who stayed in

“Building a successful company is a different skillset and goal. As in playing pool, in academia you can break and hope something goes in the pocket and you chase that. In industry, you have to call the pocket and sink the shot.”

*Dr. Shaun Coughlin*



academia, describes playing an advisory role in development of COR’s portfolio, as compared to the co-founder David Phillips, who left academia and leveraged his expertise in fibrinogen receptors to guide the development of Integrilin®, playing what Coughlin described as a “critical” role in building the company.

Academic innovators have several options about how to navigate between the worlds of academic research and entrepreneurship. On one extreme, an academic co-founder may choose to remain in academia and play the role of a board member or scientific advisor in the start-up company. On the other extreme, a co-founder may take responsibility for all aspects of developing a new company as a CEO. An intermediate option may be to assume a full-time role as a CSO or chief medical officer (CMO), in order to gain industry experience. No simple answers exist for these dilemmas. While the world of industry presents unique challenges and opportunities, academia offers more flexibility and a much greater ability to pursue basic scientific research. Transitioning to industry also requires scientists to develop enhanced people skills and business expertise, as well as becoming used to approaching innovation in a way that



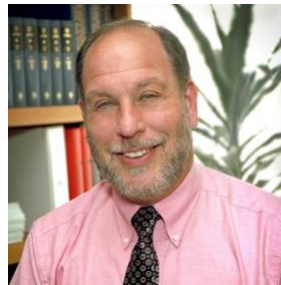
prioritizes commercial viability over scientific novelty. Some innovators may prefer to move to industry full-time, but it may also be preferable to for an academic co-founder to remain in academia and contribute to the company in an advisory capacity. Although it is considered relatively rare for scientists to return to academia from industry, Charo is an example that it is possible to revisit one's professional decisions. After working for three years at COR, Charo returned to the Gladstone Institute, where he was a professor for two decades before recently deciding to leave academia again to pursue another enterprise.

The Integrilin case also provides an interesting lesson about how a great team has to be open to pivot their strategies. Designing new molecules based on crystallography could be perceived as a more elegant method from an academic perspective, but from the point of view of industry, screening snake venoms proved to be a more practical starting point.

## *Partnerships*

“One of the lessons is that we were not particularly brilliant. We did not come up with the idea of snake venoms – we read the literature. What this says to me is that you need the right group of people... It's fairly remarkable that our little group competed and came out ahead of Merck.”

*Dr. Israel Charo*



Drug development requires the investment of considerable resources to shepherd a drug through clinical trials and FDA approval. The cost of taking a compound to the stage of an investigational new drug is approximately \$10–15 million, and another \$20 million may be required to complete a phase II study. A 2014 study found that on average, \$1.4 billion of out-of-pocket costs is necessary to bring a new prescription drug to market.<sup>17</sup>

Venture capital funding is one way for a newly founded company to obtain the funding for pre-approval drug development, but the case of COR illustrates the potential of strategic partnerships in bringing a drug to market. An early partnership with Eli Lilly provided funding that allowed eptifibatide to be developed, even though eptifibatide was not one of the compounds that Eli Lilly acquired the rights to in this partnership. Once eptifibatide was closer to approval, COR entered into a partnership with Schering-Plough to fund later-stage clinical trials in exchange for co-marketing Integrilin® in the U.S. and providing Schering-Plough with marketing rights worldwide on a royalty basis. Moreover, Schering-Plough's clinical and marketing expertise led to the inclusion of medical resource utilization data in studies of

Integrilin®, which helped Integrilin® to obtain a sizable market share despite competition from other drugs on the market.

### Reimbursement

A company's reimbursement strategy can be as important as its regulatory strategy.<sup>18</sup> It is extremely important to establish where a drug will be used and who will pay for it. Integrilin® is a drug used in the hospital setting, not a prescription medicine taken by patients at home. As such, the reimbursement for Integrilin® occurs under the diagnostic-related grouping (DRG) system. The DRG system is the method used by Medicare and some insurance companies to reimburse hospitals. In the system, a hospital is paid a fixed amount based on each patient's DRG, which reflects his or her diagnosis. If the hospital spends more than the DRG reimbursement to treat the patient, it loses money; however, if the hospital spends less than the DRG reimbursement, it makes money.

Since Integrilin® is reimbursed through the DRG system, its cost-effectiveness played a major role in its success. The placebo-controlled ESPRIT trial, conducted from June 1999 to February 2000, further demonstrated Integrilin®'s clinical effectiveness and also contained data about the utilization of medical resources that formed the basis for subsequent cost-effectiveness studies. A set of three cost-effectiveness studies published from 2000 to 2003 demonstrated that treatment with Integrilin® was ultimately more cost-

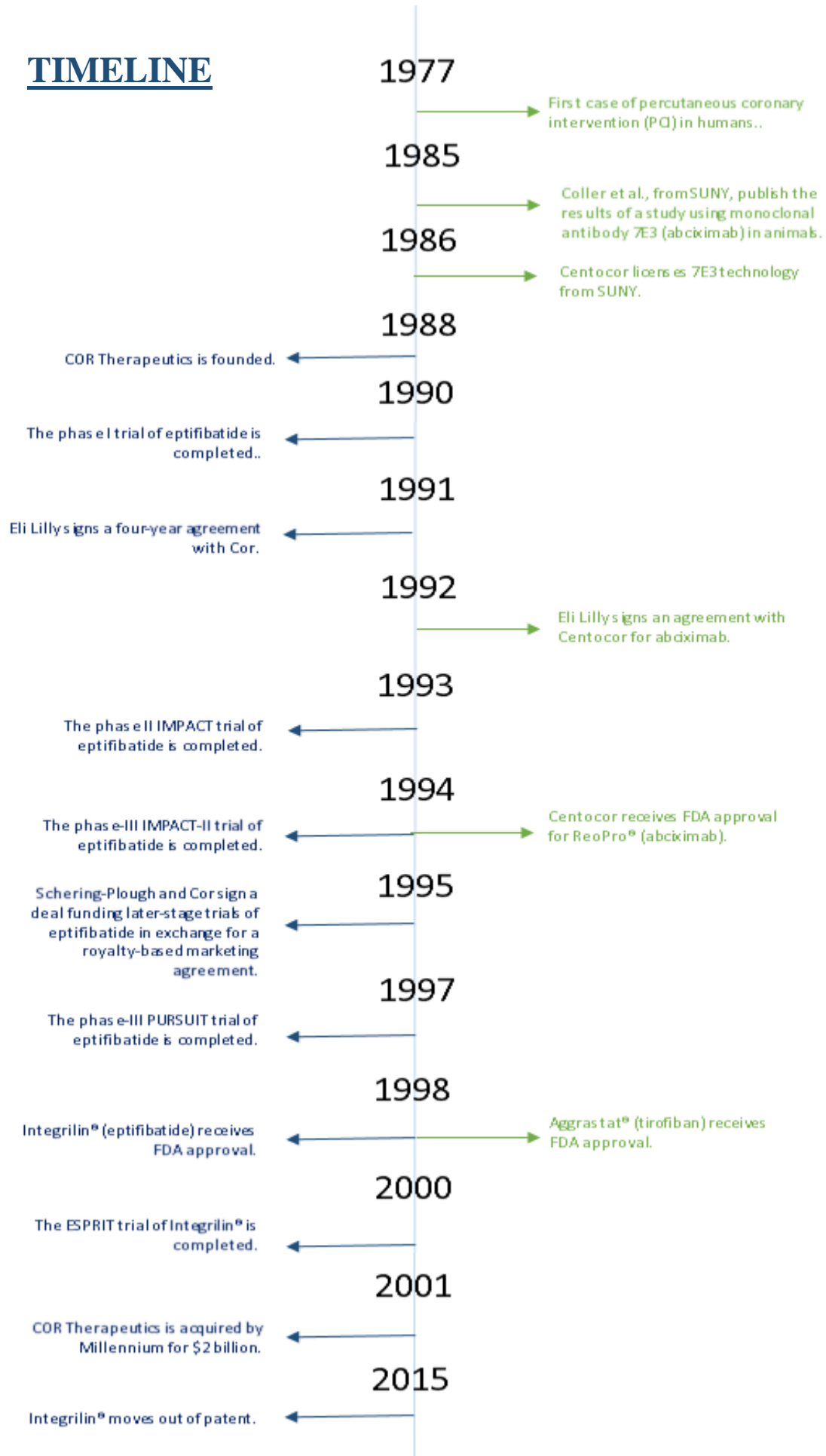
effective than stenting alone. The studies varied in terms of methodology and year of costing, but in general, Integrilin® was associated with lower acquisition costs and similar clinical outcomes when compared to ReoPro®.<sup>19</sup> As predicted by the academic founders, a 2003 study found that Integrilin® was associated with fewer complications than ReoPro®, and that Integrilin®'s incremental cost-effectiveness ratio, expressed as the cost per life-year gained, was better than that of Aggrastat® (\$21,731 vs. \$163,286).<sup>20</sup>

### References

1. Arjomand, Heidar, et al. "Percutaneous coronary intervention: historical perspectives, current status, and future directions." *American heart journal* 146.5 (2003): 787-796.
2. Jennings, S., et al. "Trends in percutaneous coronary intervention and angiography in Ireland, 2004–2011: Implications for Ireland and Europe." *IJC Heart & Vessels* 4 (2014): 35-39.
3. White, HD. "Unmet therapeutic needs in the management of acute ischemia." *The American journal of cardiology* 80.4 (1997): 2B-10B.
4. Collier, Barry S., and Lesley E. Scudder. "Inhibition of dog platelet function by in vivo infusion of F(ab')<sub>2</sub> fragments of a monoclonal antibody to the platelet glycoprotein IIb/IIIa receptor." *Blood* 66.6 (1985): 1456-1459.
5. Huang, T. F., et al. "Trigramin. A low molecular weight peptide inhibiting fibrinogen interaction with platelet receptors expressed on glycoprotein IIb-

- IIIa complex." *Journal of Biological Chemistry* 262.33 (1987): 16157-16163.
6. Gan, Z. R., et al. "Echistatin. A potent platelet aggregation inhibitor from the venom of the viper, *Echis carinatus*." *Journal of Biological Chemistry* 263.36 (1988): 19827-19832.
  7. Scarborough, Robert M., et al. "Barbourin. A GPIIb-IIIa-specific integrin antagonist from the venom of *Sistrurus m. barbouri*." *Journal of Biological Chemistry* 266.15 (1991): 9359-9362.
  8. Tcheng, James E. "Glycoprotein IIb/IIIa receptor inhibitors: putting the EPIC, IMPACT II, RESTORE, and EPILOG trials into perspective." *The American journal of cardiology* 78.3 (1996): 35-40.
  9. Gurk-Turner, Cheryle. "Glycoprotein IIb/IIIa receptor antagonists: a review of the pivotal trials." *Proceedings (Baylor University. Medical Center)* 13.2 (2000): 179.
  10. Lincoff, A. Michael, ed. *Platelet glycoprotein IIb/IIIa inhibitors in cardiovascular disease*. Springer Science & Business Media, 2003.
  11. Times Staff and Wire Reports, Los Angeles Times. June 15, 1995| [http://articles.latimes.com/1995-06-15/business/fi-13435\\_1\\_trial-results](http://articles.latimes.com/1995-06-15/business/fi-13435_1_trial-results) Accessed October 28, 2015.
  12. Phillips, David R., et al. "Effect of Ca<sup>2+</sup> on GP IIb-IIIa Interactions With Integrilin Enhanced GP IIb-IIIa Binding and Inhibition of Platelet Aggregation by Reductions in the Concentration of Ionized Calcium in Plasma Anticoagulated With Citrate." *Circulation* 96.5 (1997): 1488-1494.
  13. Eptifibatide Continues to be Successful as an Antiplatelet Agent <http://www.lgmpharma.com/blog/eptifibatide-continues-to-be-successful-as-an-antiplatelet-agent/> Accessed October 28, 2015.
  14. Egan LW. Why Physician-Scientists Are Indispensable to Cancer Research. ASCO Post. November 15, 2014. <http://www.ascopost.com/issues/november-15,-2014/why-physician-scientists-are-indispensable-to-cancer-research.aspx> Accessed October 29, 2015.
  15. I. Schafer, Ed., *The Vanishing Physician-Scientist?* Ithaca, New York: Cornell University Press. (2009).
  16. Terrett N. The Holy Grail of Drug Development: Small Molecules with the Power of Biologics. <http://www.xconomy.com/boston/2013/02/14/the-holy-grail-of-drug-development-small-molecules-with-the-power-of-biologics/> Accessed October 29, 2015.
  17. Mullin R. Cost to Develop New Pharmaceutical Drug Now Exceeds \$2.5B. *Scientific American*. <http://www.scientificamerican.com/article/cost-to-develop-new-pharmaceutical-drug-now-exceeds-2-5b/> Accessed October 28, 2015.
  18. Gold, M. "Getting reimbursement for your product in the United States." *Nature biotechnology* 21.SUP (2003): BE42-BE44.
  19. Curran M., Keating G. "Eptifibatide." *Drugs* 65.14 (2005): 2009-2035
  20. McCollam, Patrick L., David A. Foster, and Jeffrey S. Riesmeyer. "Cost and effectiveness of glycoprotein IIb/IIIa-receptor inhibitors in patients with acute myocardial infarction undergoing percutaneous coronary intervention." *American journal of health-system pharmacy* 60.12 (2003): 1251-1256.

# TIMELINE



## *Supplementary Reading*

### **Team Formation:**

- De Rubertis F, Roman F, Werner L. "Six secrets to success—how to build a sustainable biotech business." *Nature Biotechnology* 27.7 (2009): 595-597.  
<http://www.nature.com/bioent/2009/090501/full/bioe.2009.5.html>
- Steen M, Englis PD, Englis BG. "Scientific team effectiveness and the external CEO: A study of biotechnology university spin-offs." *Industry and Higher Education* 27 (2013): 15-25.  
[http://www.researchgate.net/publication/233884062\\_Scientific\\_team\\_effectiveness\\_and\\_the\\_external\\_CEO\\_A\\_study\\_of\\_biotechnology\\_university\\_spin-offs.Industry\\_and\\_Higher\\_Education](http://www.researchgate.net/publication/233884062_Scientific_team_effectiveness_and_the_external_CEO_A_study_of_biotechnology_university_spin-offs.Industry_and_Higher_Education)
- York A, McCarthy KA, Darnold TC. "Building biotechnology teams: Personality does matter." *Journal of Commercial Biotechnology* 15.4 (2009): 335-346. <http://www.palgrave-journals.com/jcb/journal/v15/n4/full/jcb200919a.html>
- Pallarito, K. "Can You Go Home Again?" - The Scientist Magazine. June 1, 2006  
<http://www.the-scientist.com/?articles.view/articleNo/24053/title/Can-You-Go-Home-Again-/>

### **Target Product Profile:**

- UCSF Launchpad - Target Product Profile Example for Drug Development  
<http://launchpad.ucsf.edu/target-product-profile-therapeutics-part-1/>
- Target Product Profile – A strategic development process tool. FDA Guide  
[www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080593.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080593.pdf)
- Lambert, WJ. "Considerations in developing a target product profile for parenteral pharmaceutical products." *AAPS PharmSciTech* 11.3 (2010): 1476-1481.  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2974137/>

### **Partnerships:**

- Cyranoski, D. Pharmaceutical futures: made in China?. *Nature News* 455.7217 (2008): 1168-1170.  
<http://www.nature.com/news/2008/291008/full/4551168a.html>
- Schachter, B. Partnering with the professor. *Nature Biotechnology* 30, 944–952 (2012)  
<http://www.nature.com/nbt/journal/v30/n10/full/nbt.2385.html>

### **Reimbursement Strategies:**

- Gold, M. "Getting reimbursement for your product in the United States." *Nature biotechnology* 21.SUP (2003): BE42-BE44.  
<http://www.nature.com/bioent/2003/030601/full/bioent738.html>

### **Unmet Need:**

- UCSF Launchpad - Unmet Needs: A specific clinical problem faced by a well-defined target population.  
<http://launchpad.ucsf.edu/keys-to-success/unmet-needs/>