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Lead discovery and optimization strategies for peptide macrocycles

Abhijit Bhat [a, *], Lee R. Roberts [b], John J. Dwyer [c]

[a] Ipsen Bioscience, Inc. 650 East Kendall Street, Cambridge, MA 02142, USA
[b] Pfizer Worldwide Medicinal Chemistry, 200 Cambridge Park Drive, Cambridge, MA 02140, USA
[c] Ferring Research Institute, 4245 Sorrento Valley Blvd., San Diego, CA 92121, USA

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ABSTRACT

Peptide macrocycles represent a chemical space where the best of biological tools can synergize with the best of chemical approaches in the quest for leads against undruggable targets. Peptide macrocycles offer some key advantages in both lead discovery and lead optimization phases of drug discovery when compared to natural product and synthetic macrocycles. In addition, they are uniquely positioned to capitalize on the therapeutic potential of peptides because cyclization can help drive selectivity, potency and overcome the common limitations of metabolic instability of peptides.

1. Introduction

A recent analysis from the Tufts Center for Study of Drug Development reveals that the number of biotech products in clinical trials has grown 155 percent in 11 years, from 355 in 2001 to 907 in 2012, with big pharmaceutical companies involved in over 40% of these programs [1]. Our analysis of development pipelines in early 2013 revealed that while 70% of the development candidates in clinical trials were small molecules, over 21% were antibodies (Fig. 1) [2]. This represents a significant shift from the singular focus on small molecule drugs primarily delivered as oral pills. While commercial factors, such as the ability to command higher prices and lower susceptibility to competition from generics, are often cited as the drivers of the growth in biotech drugs it is also recognized that the targets for biologic drugs are often outside the realm of what is considered as 'druggable' by small molecules. The shift towards biologic drugs has also increased the acceptance and representation of injectable drugs in the development pipelines. Indeed one of the most anticipated class of drugs at the moment are anti-PCSK9 mAbs for hypercholesterolemia, a primary care indication that literally created the blockbuster small molecule drug model over the past two decades [3].

There is a growing interest in pharmacologically important targets that cannot be effectively drugged by either small molecules or antibodies because of their shallow and/or extended binding interfaces or their location in the intracellular space. Medicinal chemists have become increasingly interested in macrocyclic drugs as chemical matter to overcome the targeting limitations of the prevalent modalities because the macrocycles are expected to be cell permeable like small molecules, but with an ability to modulate targets with extended binding surfaces with high selectivity and potency just like antibodies.

Macrocyclic drugs can be broadly classified into Non-peptidic and Peptidic macrocycles. The non-peptidic macrocycles can be further divided into natural product like and synthetic macrocycles. The natural product class consists of molecules that are core analogs of complex natural products. A few examples of this class include epothilones, vancomycin, erythromycin & maytansine derivatives. In general synthetic feasibility, scalability and structural ambiguity have led to the decline of representation of natural products in screening collections. Over the last decade, impressive progress has been made in diversity oriented synthesis strategies and biochemical approaches that have generated screening collections of complex natural product like libraries [4]. However these scaffolds remain challenging from lead optimization and

* Corresponding author.
E-mail addresses: abhijit.bhat@ipsen.com, abhat@outlook.com (A. Bhat), Lee.roberts@pfizer.com (L.R. Roberts), John.dwyer@ferring.com (J.J. Dwyer).

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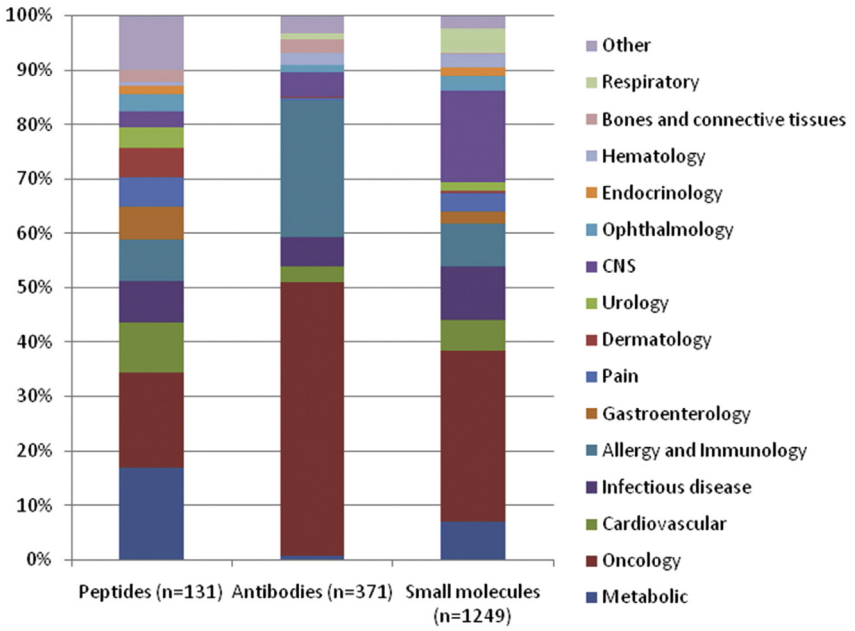

Fig. 1. Comparison of pharmaceutical development pipelines by modalities in January 2013. Source: Peptide therapeutics foundation (peptides), RBC LLC (antibodies), Sagient research (small molecules).

development perspective. Synthetic macrocycles are generally defined as non-natural cyclic molecules with a ring system made of 12 or more atoms [5]. These molecules for most part sit just outside the confines of 'Rule of five' that define the physicochemical properties of orally bioavailable small molecules with favorable ADMET profiles [6]. These macrocycles are traditionally the most attractive from a medicinal chemist's perspective for a number of reasons, the least of which is the fact that these synthetic macrocycles are often conformationally locked versions of acyclic heterocyclic molecules that the medicinal chemists are comfortable working with. There is tremendous interest in understanding the rules that govern cell permeability, oral bioavailability as well as tissue distribution and metabolic and toxicological liabilities of this class of molecules [7].There is a clear driving force to engineer these scaffolds with "small molecule" like ADMET properties thus making them possibly orally bioavailable. A number of cyclization strategies have been utilized to synthesize the macrocycles, which include lactamization, lactonization, nucleophilic displacement, Ring closing metathesis (RCM), click chemistry, thio-ene reaction and organometallic coupling reactions. However despite the versatility of synthetic tools available to create macrocycles it is important to note that it still remains a difficult task to routinely create and screen a library of synthetic macrocycles and significant efforts are underway to incorporate macrocyclic scaffolds in the corporate screening files in order to capture this under represented chemical space.

In contrast to small molecules and antibodies, there is a somewhat limited interest in developing peptide based drugs as our analysis showed that only about 7% of development candidates in 2013 were peptides even though historically peptides have fared comparably in development success rates (Fig. 2). Peptides have rich pharmacological potential as they can serve as agonists, antagonists or allosteric modulators across a wide variety of target classes and can also serve as excellent targeting agents to deliver payloads and as vehicles to create bifunctional therapeutics. Poor oral bioavailability, poor membrane permeability, susceptibility to proteolysis and short circulating half-life are often cited as limitations of peptide therapeutics.

In contrast to natural product and synthetic macrocycles, peptide macrocycles have a number of features that make them very attractive, albeit underappreciated candidates from a drug discovery perspective. Peptidic macrocycles are uniquely positioned to capitalize on the therapeutic potential of peptides because cyclization and medicinal chemistry strategies can help overcome

	1995-2004		1993-2004
	Peptide	Antibody	SM
Total number of compounds	145	227	1225
Percentage of cohort with known fates	86%	79%	80%
Cumulative success rate	14%	12%	7%
Phase 1 to 2 transition rate	83%	77%	63%
Phase 2 to 3 transition rate	31%	37%	38%
Phase 3 to review transition rate	68%	63%	61%

Fig. 2. Comparison of development outcomes of peptides, antibodies and small molecules [2].