# ARTICLE IN PRESS

ADR-12981; No of Pages 22

Advanced Drug Delivery Reviews xxx (2016) xxx-xxx



Contents lists available at ScienceDirect

## Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr



- Sharpening nature's tools for efficient tuberculosis control: A review of the potential role and development of host-directed therapies and strategies for targeted respiratory delivery:
- Gemma O'Connor <sup>a,b</sup>, Laura E. Gleeson <sup>b</sup>, Aidan Fagan-Murphy <sup>a,d</sup>, Sally-Ann Cryan <sup>a,c,d</sup>, Mary P. O'Sullivan <sup>b</sup>, Joseph Keane <sup>b,\*</sup>
  - <sup>a</sup> School of Pharmacy, Royal College of Surgeons in Ireland, Dublin 2, Ireland
    - <sup>b</sup> Trinity Centre for Health Sciences, St James's Hospital, Dublin 8, Ireland
  - <sup>c</sup> Trinity Centre for Bioengineering, Trinity College Dublin, Dublin 2, Ireland
    - <sup>d</sup> SFI Centre for Research in Medical Devices (CURAM), Dublin 2, Ireland

10

13

#### 11 ARTICLE INFO

#### Article history:

- Received 6 January 2016
- 14 Received in revised form 4 April 2016
- 15 Accepted 20 April 2016
- 16 Available online xxxx

### 29

- 32 Keywords: 33 Anti-tubercular
- 34 Immunomodulation
- 35 Vitamin
- 36 Targeted drug delivery
- 37 Microparticle
- 38 Particle engineering
- 39 Inhalation 40 Adjunctive
- 40 Adjunctive therapy 41 *In vitro*
- 42 In vivo

46 47 49

- 43 Pre-clinical testing
- Q3 Multidisciplinary

#### ABSTRACT

Centuries since it was first described, tuberculosis (TB) remains a significant global public health issue. Despite 22 ongoing holistic measures implemented by health authorities and a number of new oral treatments reaching 23 the market, there is still a need for an advanced, efficient TB treatment. An adjunctive, host-directed therapy 24 designed to enhance endogenous pathways and hence compliment current regimens could be the answer. The 25 integration of drug repurposing, including synthetic and naturally occurring compounds, with a targeted drug 26 delivery platform is an attractive development option. In order for a new anti-tubercular treatment to be pro- 27 duced in a timely manner, a multidisciplinary approach should be taken from the outset, including stakeholders 28 from academia, the pharmaceutical industry, and regulatory bodies keeping the patient as the key focus. Pre- 29 clinical considerations for the development of a targeted host-directed therapy are discussed here.

© 2016 Published by Elsevier B.V. 31

#### Contents

1.					
2.	Host-	Host-directed therapies (HDT) for tuberculosis			
	2.1.	Vitamins as host-directed therapies			
		2.1.1. Vitamin A			
		2.1.2. Vitamin D			
		2.1.3. Antioxidant vitamins			
		2.1.4. Practicalities of vitamins as HDT			
	2.2.	Other host-directed therapies			
		2.2.1. Autophagy inducers			
		2.2.2. Metabolic regulators			
		2.2.3. Eicosanoid manipulation			

E-mail addresses: gemmaoconnor@rcsi.ie (G. O'Connor), gleesole@tcd.ie (L.E. Gleeson), aidanfmurphy@rcsi.ie (A. Fagan-Murphy), scryan@rcsi.ie (S.-A. Cryan), mary.osullivan@tcd.ie (M.P. O'Sullivan), jkeane@stjames.ie (J. Keane).

http://dx.doi.org/10.1016/j.addr.2016.04.024 0169-409X/© 2016 Published by Elsevier B.V.

Please cite this article as: G. O'Connor, et al., Sharpening nature's tools for efficient tuberculosis control: A review of the potential role and development of host-directed ther..., Adv. Drug Deliv. Rev. (2016), http://dx.doi.org/10.1016/j.addr.2016.04.024

<sup>★</sup> This review is part of the Advanced Drug Delivery Reviews theme issue on "antituberculosis\_immunotherapeutics".

<sup>\*</sup> Corresponding author.

# **ARTICLE IN PRESS**

G. O'Connor et al. / Advanced Drug Delivery Reviews xxx (2016) xxx-xxx

		2.2.5.	Cytokine modulation		
		2.2.6.	Protein kinase inhibitors		
		2.2.7.	Matrix metalloproteinase inhibitors		
		2.2.8.	<i>MicroRNAs</i> ( <i>miRs</i> )		
3.	Poten	tial advar	nced formulations for targeted, respiratory delivery of host-directed therapies		
	3.1.	Formula	ation experience with HDT in clinical and non-clinical settings		
	3.2.		on devices for HDT		
	3.3.	Particle	properties and their influence on the effectiveness of inhaled therapies		
	3.4.	Particle	engineering approaches		
		3.4.1.	Microparticle-based drug delivery systems		
		3.4.2.	Lipid-based drug delivery systems		
		3.4.3.	Alternative particle engineering strategies		
4.	Precli	nical effic	acy models specific to HDT		
	4.1.		rculosis (Mtb) strain selection		
	4.2.	In vitro	models of mycobacterial infection		
		4.2.1.	Macrophages		
		4.2.2.	Dendritic cells		
		4.2.3.	Airway epithelial cells		
		4.2.4.	Neutrophils		
		4.2.5.	3-D models of Mtb infection		
		4.2.6.	Testing HDTs in combination with conventional anti-tubercular drugs		
	4.3. In		models of mycobacterial infection		
		4.3.1.	In vivo model selection		
		4.3.2.	In vivo models suitable for HDT screening in mycobacterial infection		
		4.3.3.	Obtaining and Interpretation of results following HDT treatment		
5.	Concluding remarks				
References					

#### 1. Introduction

92

93

94

95

96

97 98

gg

100

101

102 103

104

105

106

107 108

109

112 113

114

116

117

118

119

120

121

122

123

124

125

126

> Tuberculosis (TB) infection, caused by the pathogen Mycobacterium tuberculosis (Mtb), represents a global public health crisis traversing centuries. Recent figures published by the World Health Organisation (WHO) cite TB as the leading cause of death by infection alongside Human Immunodeficiency Virus (HIV), responsible for 1.5 million deaths annually [1,2]. Compounding this crisis is the rising number of drug-resistant cases of Mtb infection. Multi-drug-resistant TB (MDR-TB), defined as resistance to at least the two first-line anti-bacterials (isoniazid and rifampicin), and extensively drug-resistant Mtb (XDR-TB), characterised by additional resistance to second-line therapeutics, have complicated the already arduous treatment regimens [3]. Despite reductions in the global burden of TB following the WHO's introduction of directly observed treatment, short-course (DOTS) in the 1990s, and recently the adoption of a more holistic approach by incorporating patient care, policy, and research, the stated aim of reducing TB deaths and incidence by 90% and 80%, respectively, between 2015 and 2030 remains a substantial challenge [1,4]. The TB Alliance, established in 2000, has placed significant emphasis on the development of new combinatory regimens, and crucially, new drug candidates, by bringing organisations together using its product development partnership approach (PDP) [5]. Two new drugs, delamanid and bedaquiline, have recently been licensed for the treatment of MDR-TB. However, as with conventional anti-mycobacterials, acquired resistance to these novel agents has already been reported, emphasising the limitation of pathogendirected therapies in treating this heterogeneous and dynamic disease [6].

> Our natural defences, however, should not be underestimated. Despite one third of the world's population living with latent tuberculosis infection (LTBI), just 9.6 million people developed active disease in 2014 [1]. The host immune response to TB infection, therefore, is capable of successfully limiting infection in the majority of individuals. Thus, a logical question is how can the immune response be enhanced in patients where active disease takes hold? The concept of 'host-directed therapies' (HDT), whereby therapeutics targeting the human host's immune response to infection for the purpose of augmenting beneficial and reducing harmful features, have garnered significant international

interest, evidenced by the recent publication of several high-quality reviews on the topic [7–9]. The most obvious attraction of this approach is 129 the lower likelihood of development of treatment-resistant strains of 130 Mtb in comparison to conventional pathogen-directed therapies. 131 Additionally, HDTs hold potential in a myriad of settings—as vaccine ad-132 juncts, as prophylactic therapies for close contacts of cases, as strategies 133 to limit infectivity and shorten treatment duration, as well as improving 134 overall survival outcome and reducing the lung tissue damage resulting 135 from excessive inflammation. Furthermore, "drug repurposing" of 136 currently licensed medications has already been highlighted as an ap-137 proach to tackling the TB pandemic, given the benefits of faster market 138 access and reduced development costs [10,11]. Several drugs currently 139 licensed for other indications (some of which are also off-patent) are 140 showing promise as potential HDTs, offering affordable provision to 141 the underdeveloped economies that most require novel TB therapies. 142

The host immune response to Mtb infection, however, is layered 143 with complexity. Many immune functions that are vital early in host 144 defence prove detrimental in advanced infection [12]. Consequently, 145 in addition to agents that enhance the natural host immune response 146 to TB, a large number of anti-inflammatory agents that work through at 147 tenuation of the destructive effects of excessive immune responses are 148 also under investigation as potential HDTs. The temporal events of infection and disease progression must be understood and considered in 150 order to maximise efficacy of new therapies and, crucially, to prevent 151 undesired harmful outcomes. Additionally, several promising HDTs - 152 including vitamins that are discussed in detail in this review - have 153 been demonstrated to influence host metabolism; therefore, variable 154 host nutritional status may be important in determining the efficacy of 155 various approaches to manipulation of immune response. Genetic variations in host immunity are also likely to impact individual response to 157 HDT to a far greater extent than conventional pathogen-targeted antimicrobials [13], potentially suggesting a role for the integration of 159 pharmacogenomics and a "personalised medicine" approach into the 160 development of HDTs, tailoring therapies to an individual's "immune 161 signature" [14,15]. Although such measures at present are still consid- 162 ered novel and consequently costly for the treatment, accompanying di- 163 agnostics and multidisciplinary care, if governments and policy makers 164 truly wish to overcome this pandemic, then the potential of this 165

Please cite this article as: G. O'Connor, et al., Sharpening nature's tools for efficient tuberculosis control: A review of the potential role and development of host-directed ther..., Adv. Drug Deliv. Rev. (2016), http://dx.doi.org/10.1016/j.addr.2016.04.024

## Download English Version:

# https://daneshyari.com/en/article/8402581

Download Persian Version:

https://daneshyari.com/article/8402581

<u>Daneshyari.com</u>