International Journal of Antimicrobial Agents xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Chemotherapy of respiratory syncytial virus infections: the final breakthrough

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ARTICLE INFO

Article history:
Received 23 December 2014
Accepted 24 December 2014

Keywords:
Respiratory syncytial virus
RSV
Virus–cell fusion
Palivizumab
Ribavirin
GS-5806

ABSTRACT

Respiratory syncytial virus (RSV) infection is the leading cause of hospitalisation for children under 5 years of age and causes excess mortality in the elderly. There is still no approved vaccine available, although the disease can be curtailed by RSV-specific monoclonal antibody. The only antiviral drug approved for the treatment of RSV infection is ribavirin aerosol, but this treatment is cumbersome and its efficacy is questionable. A new antiviral, GS-5806, which interferes with virus–cell fusion, has proven efficacious in experimental RSV infections in adults.

1. Introduction

Since I reviewed the perspectives for the chemotherapy of respiratory syncytial virus (RSV) infections for the *International Journal of Antimicrobial Agents* [1], now almost 2 decades ago, little progress has been made in the prophylaxis or therapy of RSV infection, which has remained the most important respiratory infection in infants and young children [2,3]. The recent report of DeVincenzo et al. that GS-5806, which inhibits RSV fusion with the host cell, suppresses clinical disease in healthy adults experimentally infected with RSV [4] may have a significant impact on the prevention and treatment of RSV infection [5].

2. Virus–cell fusion

RSV belongs to the subfamily Pneumovirinae (family Paramyxoviridae) (Fig. 1), which for their entry into host cells depend on two viral glycoproteins, an attachment protein referred to as G and the fusion (F) glycoprotein [6]. The F glycoproteins form trimers and are referred to as class I viral fusion proteins. F initially folds to a metastable, pre-fusion conformation, and upon activation refolds to catalyse membrane fusion, resulting in the post-fusion conformation [6]. F expresses a metastable, antigenic site Ø (Fig. 2) which can be targeted by extremely potent RSV-neutralising antibodies and therefore offers great potential for vaccine development [7].

3. The importance of RSV infection

RSV infection is a particular burden in young children [2]. Most children with RSV infection are previously healthy, so that control strategies targeting only high-risk children only have a limited impact on the total disease burden of RSV infection [2]. Among infants <1 year of age, the risk of death from respiratory causes is increased by a factor of nine for infants who have RSV infection compared with those who have influenza [8]. RSV infection in early childhood may be associated with recurrent wheezing later in life [9]. Patients who have undergone haematopoietic cell transplantation are at increased risk of severe RSV infection [10,11], as are elderly patients and those with cardiac or pulmonary conditions [12–14]. In adults aged ≥50 years, hospitalisation rates for RSV (or human metapneumovirus) may be similar to those associated with influenza [14]. RSV can cause severe lower respiratory complications in older adults, resulting in respiratory failure, prolonged hospitalisation and high mortality similar to seasonal influenza [13].

4. Palivizumab

Palivizumab (Synagis®; MedImmune) was approved by the US Food and Drug Administration (FDA) in 1998 for the prevention of severe lower respiratory tract infections secondary to RSV in paediatric patients at high risk for developing disease that required hospitalisation [15]. Palivizumab is an RSV-specific monoclonal antibody that is only partially effective in reducing RSV hospitalisation rates by ca. 60% [16]. It is indicated only for the 3%

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http://dx.doi.org/10.1016/j.ijantimicag.2014.12.025
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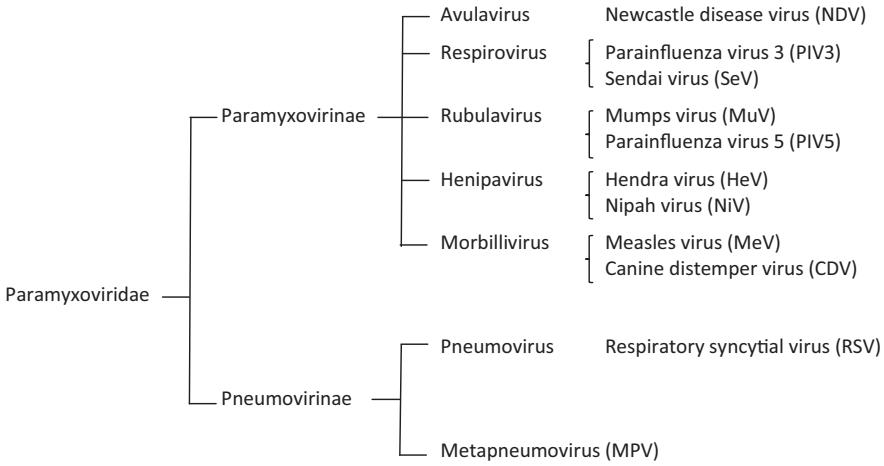

Fig. 1. Pseudophylogenetic tree of the Paramyxoviridae.

Adapted from Jardetzky and Lamb [6].

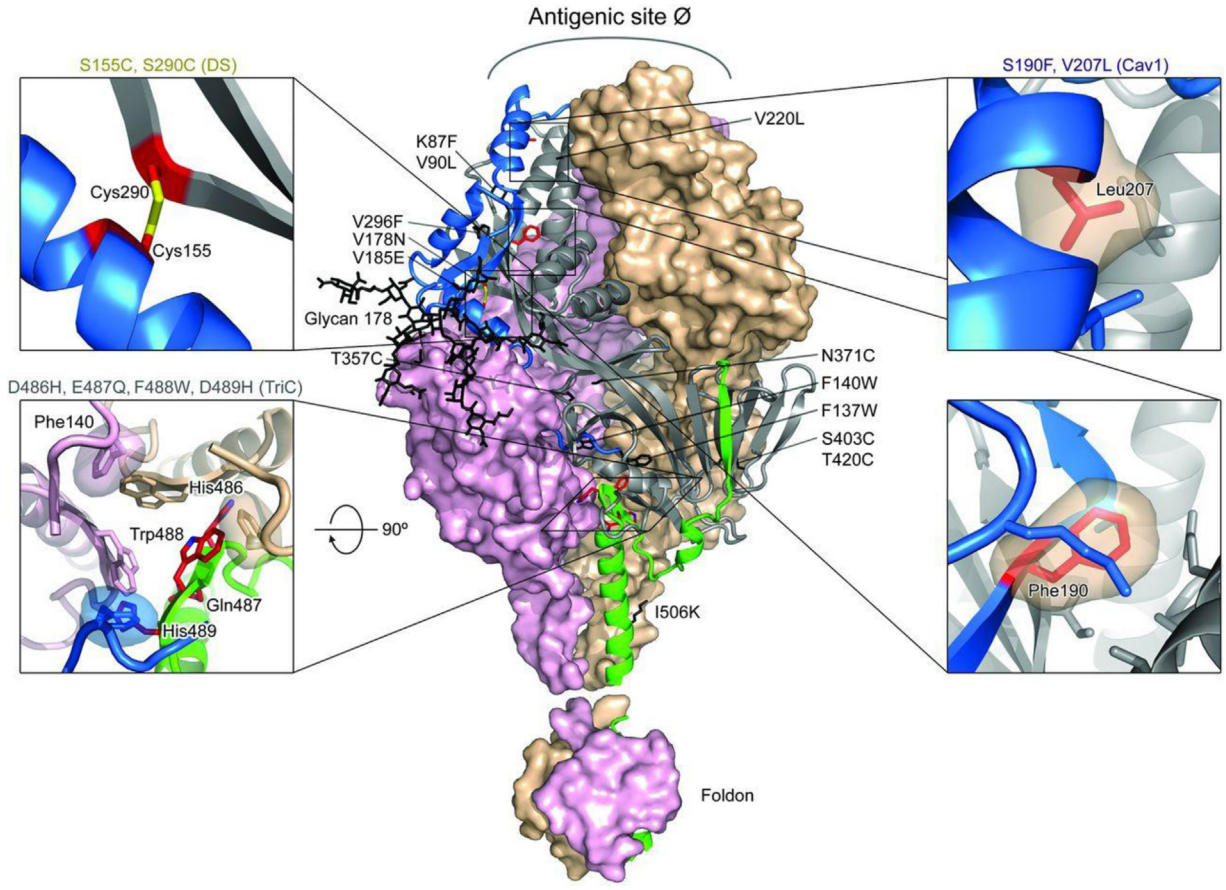

Fig. 2. Design of soluble site Ø-stabilised respiratory syncytial virus (RSV) F trimers. Over 100 variants of RSV F containing the T4 fibritin trimerisation domain (foldon) were designed to provide greater stability to antigenic site Ø. Shown here is the structure of the RSV F trimer in its D25-bound conformation with modelled C-terminal foldon. The trimer is displayed with two of the three F1F2 protomers in molecular surface representation (coloured tan and pink), and the third F1F2 protomer in ribbon representation. The ribbon is coloured grey in regions where it is relatively fixed between pre- and post-fusion, and the N- and C-terminal residues that move >5 Å between pre- and post-fusion conformations are coloured blue and green, respectively. Mutations compatible with RSV F expression and initial D25 recognition, but insufficiently stable to allow purification of RSV F as a homogeneous trimer, are labelled and shown in stick representation (coloured black). Insets show enlargements of stabilising mutations in stick representation (coloured red) for DS, Cav1 and TriC variants, all of which sufficiently stabilise antigenic site Ø to allow purification as a homogeneous trimer. According to McLellan et al. [7]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of the total infant population who are born prematurely or who have underlying conditions (chronic lung disease, congenital heart disease, immunodeficiencies or other severe chronic illnesses) [17]. RSV infection in early childhood is associated with recurrent wheezing later in life [9], and palivizumab treatment in otherwise healthy preterm infants results in a significant reduction in wheezing during the first year of life, even after the end of treatment [9].

Palivizumab is the only product approved for the prevention of serious RSV disease [17] and, based on seven studies (all

Please cite this article in press as: De Clercq E. Chemotherapy of respiratory syncytial virus infections: the final breakthrough. Int J Antimicrob Agents (2015), http://dx.doi.org/10.1016/j.ijantimicag.2014.12.025