pyelonephritis (APN), associated with an elevated MYC and TCR expression but an unresponsive innate immune system. In contrast, asymptomatic carriers showed an innate immune response profile with modest activation of *IRF7*-dependent genes and low MYC expression.

The genetic basis for this discrepancy was examined in the murine pyelonephritis model, where *Irf7* was identified as a key regulator of MYC expression, with pronounced inhibition of MYC in *Irf7*$^{-/-}$ mice that were protected from pathology.

According to the present disclosure there is provided a therapeutic agent comprising a bacteria which expresses an inhibitor of MYC activity or a extract or product obtainable therefrom, for use in the prevention or treatment of disease wherein MYC levels are elevated.

In one aspect, there is provided a therapeutic agent comprising a supernatant produced during culture of a bacteria which expresses and secretes a bacterial factor that is an inhibitor of MYC activity, or a bacterial factor isolated from the supernatant, which inhibits MYC activity, for use in the prevention or treatment of cancer and/or infection.

The applicants have found that certain bacteria, in particular certain uropathogenic bacteria inhibit MYC activity in a host, and that this is caused by expression of a bacterial factor, which appears to be secreted by the bacteria, and thus is present in supernatants. Thus in a particular embodiment, the therapeutic agent comprises an extract of product obtainable from bacteria, which comprises or is derived from a supernatant produced during culture of the bacteria.

Furthermore, they have identified that the mechanism by which the bacteria and in particular the factor obtainable from the bacteria exerts its effect. The identified mechanism has been found to comprises a direct inhibitory effect of bacteria on mucosal MYC expression, due to a new class of virulence factors encoded on PAI I in uro-pathogenic *E. coli* strains. The findings suggest a scenario where mucosal MYC expression is regulated downstream of *Irf3* and *Irf7*, which are major determinants of disease severity and susceptibility in infected kidneys and that

MYC is targeted by specific bacterial genes on pathogenicity islands that are shared by uropathogenic *E. coli* strains.

Furthermore, the applicants have found that MYC may be degraded by a second strategy, in which activation of CK1α1 And IFNβ dependent mechanisms of phosphorylation and proteasomal degradation by the host is triggered.

The isolated factors are novel and so these form a further example of the disclosure.

Thus according to the present disclosure there is provided an inhibitor of MYC activity comprising a factor obtainable from a bacteria. In another aspect, there is provided an inhibitor of MYC activity comprising a bacterial factor obtainable from a bacterial supernatant produced during culture. In particular, the bacteria is a pathogenic bacteria, such as a uropathogenic E. coli. Particular examples of such uropathogenic E. coli is selected from CFT073 and 536.

As used herein, the expression 'inhibitor of MYC activity' refers to any entity which controls, regulates or limits the activity of the MYC transcription factor, in particular *in vivo* in mammals. This may be achieved for example by direct inhibition of the MYC protein, by downregulation of the c-Myc gene *in vivo*, or by interfering with any pathway in which MYC is involved.

Bacteria can evolve by modification of the pre-existing genome sequence, acquisition or loss of genetic information. Gene acquisition by horizontal gene transfer, involving mobile genetic elements like plasmids or genomic islands (GEIs), increases the capacity of bacteria to evolve and adapt to new environments.

The pathogenic properties of bacteria are correlated to the expression of virulence- or disease-associated factors, that are

For administration to patients, the inhibitor or bacteria is suitably administered in the form of a pharmaceutical composition, which further comprise a pharmaceutically acceptable carrier. Such compositions form a further example of the disclosure.

Thus according to a third aspect of the present disclosure there is provided a pharmaceutical composition comprising a therapeutic agent as defined herein, or an isolated inhibitor as defined herein, in combination with a pharmaceutically acceptable carrier.

In another aspect, there is provided an isolated inhibitor as described herein or a pharmaceutical composition as described herein, for use in treating or preventing cancer and/or infection.

In another aspect, there is provided a use of a therapeutic agent comprising a supernatant produced during culture of a bacteria which expresses and secretes a bacterial factor that is an inhibitor of MYC activity, or a bacterial factor isolated from the supernatant, which inhibits MYC activity,in the manufacture of a medicament for the prevention or treatment of cancer and/or infection.

In another aspect, there is provided a use of an isolated inhibitor as described herein or a pharmaceutical composition as described herein in the manufacture of a medicament for treating or preventing cancer and/or infection.

Suitable pharmaceutical compositions will be in either solid or liquid form. They may be adapted for administration by any convenient route, such as parenteral, oral or topical administration or for administration by inhalation or insufflation. The pharmaceutical acceptable carrier may include diluents or excipients which are physiologically tolerable and compatible with the active ingredient.

Parenteral compositions are prepared for injection, for example either subcutaneously or intravenously. They may be liquid solutions or suspensions, or they may be in the form of a solid that is suitable for solution in, or suspension in, liquid prior to injection. Suitable diluents and excipients are, for example, water, saline, dextrose, glycerol, or the like, and combinations thereof. In addition, if desired the compositions may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, stabilizing or pH-buffering agents, and the like.

Oral formulations will be in the form of solids or liquids, and may be solutions, syrups, suspensions, tablets, pills, capsules, sustained-release formulations, or powders. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate, and the like.

Claims

1. A therapeutic agent comprising a supernatant produced during culture of a bacteria which expresses and secretes a bacterial factor that is an inhibitor of MYC activity, or a bacterial factor isolated from the supernatant, which inhibits MYC activity, for use in the prevention or treatment of cancer and/or infection.

2. A therapeutic agent for use according to claim 1, wherein the bacteria is an attenuated uropathogenic bacteria, or a recombinant bacteria comprising an asymptomatic bacteriuria (ABU) strain which has been engineered to express an inhibitor of MYC activity obtainable from a uropathogenic strain, preferably wherein the attenutated uropathogenic bacteria is an E. coli strain, more preferably wherein the bacteria is selected from CFT073 and 536E.

3. A therapeutic agent for use according to claim 1 or claim 2, wherein the disease is cancer, preferably wherein the cancer is an epithelial or mucosal cancer.

4. An inhibitor of MYC activity comprising a bacterial factor obtainable from a bacterial supernatant produced during culture.

5. A therapeutic agent of any of claims 1 to 3, or an inhibitor according to claim 4, wherein the bacteria is a uropathogenic E. coli, preferably wherein the uropathogenic E. coli is selected from CFT073 and 536.

6. A therapeutic agent of any of claims 1 to 3, or an inhibitor according to claim 4 or 5, which comprises a protein or RNA expressed by a gene found in a PAI I or PAI II region of the genome of said bacteria.

7. A therapeutic agent or an inhibitor according to claim 6 wherein the gene is a gene found in the PAI I region of the genome, preferably wherein the PAI I region is represented by SEQ ID NO 1.

8. A therapeutic agent or an inhibitor according to any one of claims 4 to 7 which comprises a bacterial ABC transporter protein, a periplasmic binding protein, or an active fragment of either of these.

9. A therapeutic agent according to any of claims 1 to 3, or an inhibitor according to claim 4 which comprises SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4 or an active fragment thereof.

10. A therapeutic agent or an inhibitor according to claim 9 which is a miRNA molecule.

11. A pharmaceutical composition comprising a therapeutic agent as defined in any one of claims 1 to 10, or an isolated inhibitor according to any one of claims 4 to 10, in combination with a pharmaceutically acceptable carrier.

12. An isolated inhibitor according to any one of claims 4 to 10 or a pharmaceutical composition according to claim 11, for use in treating or preventing cancer and/or infection.

13. An isolated inhibitor or pharmaceutical composition for use according to claim 12 wherein the disease is cancer.

14. An isolated inhibitor or pharmaceutical composition for use according to claim 13 wherein the cancer is an epithelial or mucosal cancer.

15. Use of a therapeutic agent comprising a supernatant produced during culture of a bacteria which expresses and secretes a bacterial factor that is an inhibitor of MYC activity, or a bacterial factor isolated from the supernatant, which inhibits MYC activity,in the manufacture of a medicament for the prevention or treatment of cancer and/or infection.

16. The use according to claim 15, wherein the bacteria is an attenuated uropathogenic bacteria, or a recombinant bacteria comprising an asymptomatic bacteriuria (ABU) strain which has been engineered to express an inhibitor of MYC activity obtainable from a uropathogenic strain, preferably wherein the attenutated uropathogenic bacteria is an E. coli strain, more preferably wherein the bacteria is selected from CFT073 and 536E.

17. The use according to claim 15 or 16, wherein the disease is cancer, preferably wherein the cancer is an epithelial or mucosal cancer.

18. The use according to any one of claims 15 to 17, wherein the bacteria is a uropathogenic E. coli, preferably wherein the uropathogenic E. coli is selected from CFT073 and 536.

19. The use according to any one of claims 15 to 18, wherein the therapeutic agent comprises a protein or RNA expressed by a gene found in a PAI I or PAI II region of the genome of said bacteria.

20. The use according to claim 19, wherein the gene is a gene found in the PAI I region of the genome, preferably wherein the PAI I region is represented by SEQ ID NO 1.

21. The use according to any one of claims 18 to 20, wherein the therapeutic agent comprises a bacterial ABC transporter protein,

a periplasmic binding protein, or an active fragment of either of these.

22. The use according to any one of claims 15 to 17, wherein the therapeutic agent comprises SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4 or an active fragment thereof.

23. The use according to claim 22, wherein the therapeutic agent is a miRNA molecule.

24. Use of an isolated inhibitor according to any one of claims 4 to 10 or a pharmaceutical composition according to claim 11 in the manufacture of a medicament for treating or preventing cancer and/or infection.

25. The use according to claim 24, wherein the disease is cancer.

26. The use according to claim 25, wherein the cancer is an epithelial or mucosal cancer.