which regulate gene expression. These changes meant that *MYC* gene expression could be activated without Brd4.

Rathert *et al.* also found that genes associated with the Wnt-signalling pathway, a known driver of tumour development, were upregulated in resistant cells. Wnt activation was sufficient to promote JQ1 resistance, possibly by driving the transcription of *MYC* at an enhancer generated specifically in the resistant cells (Fig. 1). Finally, the authors found the same mechanism of resistance to JQ1 in some other cancer types and in blood cells taken from people with leukaemia. Together, their data suggest that the usefulness of BET inhibitors could be expanded by combining them with Wnt-pathway inhibitors.

Taking a different approach, Fong *et al.*[5] rendered mouse AML cells resistant to BET inhibition by continuously exposing these cells to another BET inhibitor, eventually yielding drug-resistant clonal populations. This experiment also showed that Wnt activation has a role in drug resistance. Furthermore, the resistant cells had features of stem cells, suggesting that the AML cancer-stem-cell population, or a subset thereof, does not respond to BET inhibitors.

The Wnt pathway has previously been shown to be involved in drug resistance in AML cancer stem cells[9]. Moreover, the drug-resistant nature of cancer stem cells is well established[10]. However, Rathert and colleagues did not find evidence that the resistant AML cells had stem-cell features — a distinction between the two reports.

In the current study, Shu *et al.*[6] explored BET inhibition in human breast cancer. By profiling a panel of breast-cancer cell lines, they observed that one cancer subtype — 'triple-negative' breast cancer — was sensitive to BET inhibition. Like Fong *et al.*, the authors modelled acquired resistance to BET inhibition by culturing sensitive triple-negative cells in JQ1, and then characterized emergent resistant cells. Resistant cells remained dependent on BRD4, but this dependence did not involve the protein's bromodomains.

A widely active transcriptional regulator protein called MED1 bound more tightly to BRD4 in resistant cells than in sensitive cells. The authors attributed this tighter binding to increased BRD4 phosphorylation mediated by the enzyme casein kinase 2 (CK2). The binding gave rise to bromodomain-independent, BRD4-mediated transcriptional activation of *MYC*, among other genes (Fig. 1). These data suggest that using a combination of CK2 and BET inhibitors to treat triple-negative breast cancer might prevent drug resistance.

Although many previous studies have demonstrated the efficacy of drugs against triple-negative breast cancer in animal and cell-based models, it is worth noting that these drugs have so far failed to combat tumours in people. As such, optimism should be tempered.

Collectively, these three reports show that

BET inhibitors might have a broader potential than had previously been realized. They also highlight the possibility that BET inhibitors could be used in combination with other drugs to overcome both innate and acquired drug resistance. Although the reported resistance mechanisms seem to reflect an adaptation to drug pressure, the root cause of resistance remains unknown. Does a specific mutation cause Wnt or CK2 activation, or are these adaptive changes that drive resistance through reversible epigenetic mechanisms? A complete mechanistic understanding of resistance remains to be defined.

It is important to note that clinical inhibitors of Wnt or CK2 have yet to be developed. Therefore, the hypotheses that emerge from these studies cannot be tested in the clinic. Nonetheless, these three reports provide a good foundation on which to build a better

understanding of mechanisms of resistance that should be anticipated in the clinic. ∎

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1. Klijn, C. *et al. Nature Biotechnol.* **33,** 306–312 (2015).
2. Lackner, M. R., Wilson, T. R. & Settleman, J. *Future Oncol.* **8,** 999–1014 (2012).
3. Baylin, S. B. & Jones, P. A. *Nature Rev. Cancer* **11,** 726–734 (2011).
4. Rathert, P. *et al. Nature* **525,** 543–547 (2015).
5. Fong, C. Y. *et al. Nature* **525,** 538–542 (2015).
6. Shu, S. *et al. Nature* **529,** 413–417 (2016).
7. Eilers, M. & Eisenman, R. N. *Genes Dev.* **22,** 2755–2766 (2008).
8. Qi, J. *Cold Spring Harb. Perspect. Biol.* **6,** a018663 (2014).
9. Wang, Y. *et al. Science* **327,** 1650–1653 (2010).
10. Singh, A. & Settleman, J. *Oncogene* **29,** 4741–4751 (2010).

EPIDEMIOLOGY

# A global picture of melioidosis

Comprehensive mapping and modelling have estimated global deaths from the bacterial disease melioidosis to be comparable to deaths from measles and substantially greater than those from dengue or leptospirosis.

**BART J. CURRIE & MIRJAM KAESTLI**

The bacterium *Burkholderia pseudomallei* is found in soil and water and causes the disease melioidosis in humans and animals. It was upgraded to a Tier 1 Select Agent by the US Centers for Disease Control and Prevention in 2012 — the designation given to pathogens considered of highest risk. This concern is based on a mortality rate of up to 40%, the fact that *B. pseudomallei* can be easily aerosolized in laboratory studies, its intrinsic resistance to standard antimicrobial agents and the lack of a vaccine. Writing in *Nature Microbiology*, Limmathurotsakul *et al.*[1] compile global literature on cases of melioidosis in humans and animals, and on the environmental presence of *B. pseudomallei*. The authors combine these data with environmental and demographic parameters in a modelling framework to predict countries in which melioidosis is probably endemic, and to estimate the global burden of the disease.

Melioidosis was first described in 1912 as a septicaemic disease in morphine addicts in Yangon, Myanmar. It is now recognized as a major cause of fatal pneumonia and sepsis in Thailand, Malaysia, Singapore and northern Australia[2]. Limmathurotsakul *et al.* report that melioidosis is, in fact, known to be endemic

in 48 countries spanning the tropics and including nations in East and South Asia, the Middle East, Africa, Latin America, the Caribbean and the Pacific. Furthermore, the authors' modelling suggests that melioidosis is severely under-reported in most of these countries and is probably endemic in another 34 countries that so far have had no confirmed cases.

The authors' estimate for total global human cases for 2015 was 165,000 (a 95% credible interval of 68,000–412,000), with 89,000 deaths (95% credible interval 36,000–227,000). As the authors point out, the global mortality estimates are comparable to those due to measles and much higher than those due to leptospirosis and dengue infection. That melioidosis is so badly underdiagnosed is not surprising, because most cases occur in resource-poor countries that have large rural populations and limited or no capacity for microbiological laboratory diagnosis — most crucially, the ability to culture blood samples and identify recovered bacteria.

Limmathurotsakul and colleagues' comprehensive investigation resulted in a database of 22,338 geographically located records of cases of human and animal melioidosis and the presence of environmental *B. pseudomallei*, reported between 1910 and 2014. The listing of 48 endemic countries is

**Figure 1 | Environments conducive to *Burkholderia pseudomallei* success.** The bacterial agent of the disease melioidosis has been cultivated from environments as diverse as rice paddies in Cambodia (left) and waterholes in northern and central Australia (right).

based on confirmed cases or the presence of environmental *B. pseudomallei*, but the predictions of global case numbers, deaths and endemicity are based on modelling using these data.

To predict the global population at risk, the authors used a statistical model known as a boosted regression tree to link various environmental conditions to the confirmed presence of *B. pseudomallei*. As the authors note, such models have been used to map the global burden of dengue infection[3]. The authors then used their model to assess the environmental suitability for *B. pseudomallei* globally; this predicted the bacterium to be ubiquitous throughout the tropics. The global incidence of melioidosis cases was predicted using a negative binomial model that assessed the association between melioidosis incidence rates from 16 reports from endemic locations and the predicted environmental suitability for *B. pseudomallei*, as well as further population-based parameters, including the prevalence of diabetes (the major risk factor for melioidosis).

Although *B. pseudomallei* can survive and thrive in diverse environments (Fig. 1), this does not mean that it is actually present in all the predicted locations. Studies of microbial biogeography have revealed the complexity of global dispersal patterns, with variable influences of habitat, geographical boundary, historical timescale, anthropogenic impact and organism dispersal ability[4]. Each of these factors has relevance for *B. pseudomallei*. Phylogeographic reconstruction of *B. pseudomallei* genomes supports an Australian origin for the species from an ancestral strain of *Burkholderia* in the local environment, with possibly a single introduction event into southeast Asia that was estimated to have occurred during the last glacial period (between 16,000 and 225,000 years ago)[5]. More-recent

dissemination to Africa and the Americas is hypothesized, but the timelines and modes of dispersal are unclear.

The expansion of known endemic locations for melioidosis in recent years may mostly reflect the fact that improved diagnostics have unmasked a long-standing presence of *B. pseudomallei* in the local environment. Alternatively, there may have been substantial dissemination as a result of increasing human, animal, plant and soil movements. Global warming may also hasten expansion of the endemic boundaries of the disease[6]. Reports from Brazil, Madagascar and Papua New Guinea suggest that melioidosis may be restricted to regional hotspots in some endemic countries. This may reflect under-ascertainment or environmental determinants yet to be elucidated, or that the bacterium hasn't yet dispersed widely in those countries.

Another consideration is that different melioidosis-endemic locations may vary in their specific ecological niches for *B. pseudomallei*, with the bacterium potentially providing a biodefence function for local cohabiting plant species. In addition, some introduced plants, such as pasture grasses, have been shown to become heavily colonized by *B. pseudomallei*[7]. Modelling environmental parameters from one region may not necessarily predict findings in another. Limmathurotsakul and colleagues' environmental-suitability model did show maximum rainfall rather than average rainfall or temperature to be the most important model contributor. This reflects the distinctive seasonal rainfall pattern of a tropical wet–dry climate, which is seen in the regions of Thailand and Australia that have the highest documented incidences of melioidosis, but not in Singapore. Salinity has been reported to be a negative predictor of *B. pseudomallei* presence[8], but this is in contrast to the model's findings.

Other uncertainties surround the disease itself. It is not clear what proportion of melioidosis cases result from inhalation compared with infection through the skin[6]. Epidemiological reports suggest that increased inhalation-derived infections occur during severe weather events such as cyclones and typhoons[6], and ingestion of *B. pseudomallei* from unchlorinated water seems to have more impact than previously thought[9].

As well as predicting the endemicity of melioidosis in many countries in which the disease has not yet been recorded, Limmathurotsakul and colleagues' modelling predicts incidence rates of, for example, more than 50,000, 20,000 and 13,000 annual undiagnosed cases in India, Indonesia and Nigeria, respectively. Targeted surveillance, together with support for improved regional microbiology facilities, are needed to reveal the accuracy of these predictions[10]. ■

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1. Limmathurotsakul, D. *et al. Nature Microbiol.* **1,** 15008 (2016).
2. White, N. J. *Lancet* **361,** 1715–1722 (2003).
3. Bhatt, S. *et al. Nature* **496,** 504–507 (2013).
4. Martiny, J. B. H. *et al. Nature Rev. Microbiol.* **4,** 102–112 (2006).
5. Pearson, T. *et al. BMC Biol.* **7,** 78 (2009).
6. Currie, B. J. *Semin. Respir. Crit. Care Med.* **36,** 111–125 (2015).
7. Kaestli, M. *et al. Environ. Microbiol.* **14,** 2058–2070 (2012).
8. Inglis, T. J. J. & Sagripanti, J. L. *Appl. Environ. Microbiol.* **72,** 6865–6875 (2006).
9. Limmathurotsakul, D. *et al. PLoS Negl. Trop. Dis.* **7,** e2072 (2013).
10. Dance, D. A. B. *Clin. Infect. Dis.* **60,** 251–253 (2015).