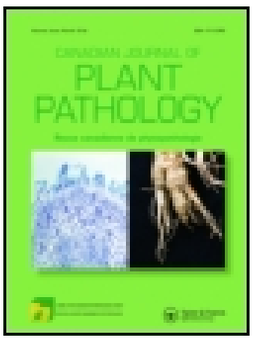

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# Building on a foundation: advances in epidemiology, resistance breeding, and forecasting research for reducing the impact of fusarium head blight in wheat and barley

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Reviews and symposia articles/articles de revue

# Building on a foundation: advances in epidemiology, resistance breeding, and forecasting research for reducing the impact of fusarium head blight in wheat and barley

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**Abstract:** Fusarium head blight (FHB) is a major fungal disease that contributes to severe economic losses for wheat and barley production in Canada and other parts of the world. Rapid developments in molecular biology over the past three decades have improved the ability to devise predictive management tools to combat the effects of the disease. Important aspects of *Fusarium* species in terms of the epidemiology associated with FHB in wheat and barley have been reported. The role of mycotoxin production in the epidemiology of the disease is beginning to receive much needed research attention. Evolutionary factors and the use of fungicides have resulted in more virulent forms of the FHB pathogens. Advances in next-generation sequencing technologies, including whole genome sequencing (WGS), genome-wide association studies (GWAS), genotyping by sequencing (GBS) and RNA sequencing (RNA-Seq) have facilitated the selection of resistant-breeding lines through marker-assisted selection. Many quantitative trait loci (QTL) associated with moderate disease resistance have been identified in wheat and barley. Changes in weather conditions play an important role in FHB epidemics and dissemination, thus a systematic and long-term research approach is needed to provide effective forecasting and risk assessment models. This review discusses the history and epidemiology of FHB pathogens in wheat and barley at the global level, as well as potential plant defence mechanisms, the recent progress made in resistance breeding, and modern tools utilized in disease prediction. It also provides future directions for improving the management of the disease with these two important cereals.

**Keywords:** barley, cereals, *Fusarium graminearum*, mycotoxins, plant breeding, plant defence, population genetics, QTL, resistance genes, wheat

**Résumé:** La brûlure de l'épi causée par le fusarium (BEF) est une grave maladie qui entraîne de lourdes pertes financières dans la production de blé et d'orge au Canada et ailleurs dans le monde. Des avancées rapides dans le domaine de la biologie moléculaire au cours des trois dernières décennies ont contribué à améliorer la capacité de concevoir des outils de gestion prévisionnelle pour lutter contre les effets de la maladie. Des aspects importants relatifs aux espèces de *Fusarium* en matière d'épidémiologie associée à la maladie chez le blé et l'orge ont été rapportés. Le rôle de la production de mycotoxines dans l'épidémiologie de la maladie commence à recevoir une attention toute particulière sur le plan de la recherche. Des facteurs d'évolution et l'utilization de fongicides ont provoqué l'apparition de formes plus virulentes d'agents pathogènes de la BEF. Des percées dans le domaine des technologies de séquençage de prochaine génération, y compris le séquençage du génome entier (WGS), les études d'association pangénomique (GWAS), le génotypage par séquençage (GBS) et le séquençage de l'ARN (RNA-Seq), ont facilité le choix de lignées de sélection résistantes grâce à la sélection assistée par marqueurs. Plusieurs locus à caractère quantitatif (QTL) associés à une résistance modérée à la maladie ont été détectés chez le blé et l'orge. Des changements dans les conditions météorologiques jouent un rôle important dans les épidémies de BEF et sa dissémination et, en

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conséquence, une voie de recherche systématique et à long terme est essentielle pour mettre au point des modèles de prévision et d'évaluation des risques. Cette revue traite de l'histoire et de l'épidémiologie des agents pathogènes de la BEF chez le blé et l'orge à l'échelle mondiale ainsi que des mécanismes potentiels de défense chez la plante, des récents progrès accomplis dans le domaine de la sélection en vue de la résistance et des outils modernes utilisés pour prédire la maladie. Il présente aussi des orientations futures pour améliorer la gestion de la maladie chez ces deux importantes céréales.

**Mots clés:** Orge, céréales, *Fusarium graminearum*, mycotoxines, sélection, mécanismes de défense des végétaux, génétique des populations, QTL, gènes de résistance, blé

## Introduction

Fusarium head blight (FHB) has been proven to be a devastating disease that represents enormous economic impacts to wheat (*Triticum aestivum* L.) and barley (*Hordeum vulgare* L.) production. While the disease is common in most cereal-producing regions of the world, it has proven to be extremely challenging to control. While yield loss can occur under epidemic conditions, the greatest effect of FHB occurs via the negative impact on grain quality due to the presence of mycotoxins. Very minute mycotoxin levels are often enough to render grains unfit for human (Health Canada 2018) or animal (Canadian Food Inspection Agency 2017) consumption. This disease is a global problem, and, in the major cereal production regions of Canada, FHB has been a major downgrading factor on grain sales for multiple decades (Gilbert and Tekauz 2000; Tekauz et al. 2000). Researchers from many countries have collected an enormous knowledge base for improved understanding of this disease.

In this manuscript, pathogen populations of wheat and barley are reviewed in terms of their genetic diversity, mycotoxin profile dynamics (*i.e*. chemotypes), and evolutionary characteristics. Due to their high toxicity at low concentrations, mycotoxins associated with FHB are heavily monitored (Bianchini et al. 2015) and are a strong focus of research. The lifecycle of the fungus and infection processes in wheat and barley have been evaluated. The trophic dynamics of this hemi-biotrophic pathogen are described by the initial biotrophic phase that is observed shortly after infection, through transition to necrotrophy. Major cultural practices that affect FHB epidemiology include the tillage method, previous crop used in rotation, and genetic characteristics of the given cultivar, as well as the reported role of mycotoxins produced by *Fusarium* species associated with FHB. This review analyzes the cereal host response to the fungus at the physical and molecular levels, as well as in terms of the toxin-specific response. Breeding efforts and processes used to design FHB-resistant wheat and barley cultivars are reviewed here. Numerous quantitative trait loci (QTL) for FHB resistance and lower deoxynivalenol (DON) accumulation (<2 ppm for wheat in Canada; <1.5 ppm in Europe; <0.5 ppm for malting barley) are discussed for barley and wheat (Foroud et al. 2019a).

While QTL have been identified and are being incorporated into elite backgrounds, a large portion of the genetic variance for resistance is controlled by numerous genes that present small effects that may also be environmentally specific. Plant breeders who are focusing on FHB resistance will be challenged to continue advancement in breeding cultivars with enhanced resistance. New biotechnological tools available to cereal breeders are outlined that offer promise, including the application of genome-wide molecular markers for association mapping and/or genomic selection. Molecular insights through a number of transcriptomic and proteomic analyzes provide a basis for the biological understanding and best application of genomics tools in crop design. At present, progress is being made in developing diagnostic tools that use environmental data for disease forecasting and management. Field-based diagnostic tools and web-based interfaces that integrate environmental and weather variables are used as models for FHB forecasting. The relationship between DON occurrence, weather variables, and disease incidence around the period of anthesis is also important when developing models for disease forecasting. The various successes of new biotechnologies are reviewed in the context of this disease, including trans-genetics, gene editing, and the application of RNA interference (RNAi) for disease reduction. Significant research undertakings have been carried out to reduce the amounts of mycotoxins in food and animal feed, where new technologies will help to build on the past endeavours and increase precision. While significant efforts will be required to develop the management of FHB further, the nutritive value of these cereal crops, combined with consumer preferences, dictates this management as a requirement for cultivation.

## The pathogen

### Fusarium *species causing FHB in wheat and barley*

FHB is attributable to a number of *Fusarium* species (Parry et al. 1995). In wheat, these include the following:

*F. graminearum* species complex (FGSC), *F. culmorum, F. avenaceum, F. poae, F. sporotrichioides, F. equiseti, F. cerealis*, and *F. verticilloides* (Sarver et al. 2011; Becher et al. 2013). Members of the FGSC, also referred to *F. graminearum* sensu lato, have been reported to be the most important FHB causative agents for wheat on a global scale (van der Lee et al. 2015). Fifteen members of the FGSC have been formally described in terms of their species (Ward et al. 2002; O'Donnell et al. 2008; Sarver et al. 2011). In North America, *F. graminearum* sensu stricto, the most abundant member of the FGSC, is regarded as the primary aetiological agent of FHB (Ward et al. 2008), while *F. graminearum, F. avenaceum, F. culmorumi*, and *F. poae* are the most abundant species for wheat in Europe (Waalwijk et al. 2003). Reports that are more recent have shown that *F. graminearum* is becoming the major cause of FHB in most European countries (Talas et al. 2011; Boutigny et al. 2014; Beyer et al. 2014). The *Fusarium* species distribution for FHB in wheat in Asia is strongly correlated with the geographic area. In Japan, *F. graminearum* is most prevalent in wheat fields in the northern parts of the country, which feature low temperatures, while *F. asiaticum* is the most abundant species in the southern region, which features higher temperatures (Suga et al. 2008). Similar results with respect to geography have been obtained in China, where approximately 76% of isolates obtained from wheat in the northeast parts of the country were of the *F. graminearum* species, while 97% of isolates collected from the southern region were of the *F. asiaticum* species (Zhang et al. 2010; Qiu et al. 2016). Surveys undertaken in Argentina, Brazil, and Uruguay have also shown *F. graminearum* to be the major causative pathogen (Ramirez et al. 2007; Reynoso et al. 2011; Castañares et al. 2014; Yerkovich et al. 2020). *Fusarium graminearum, F. poae*, and *F. chlamydosporum* were obtained from wheat in Kenya (Wagacha et al. 2010), while a new species (*F. aethiopicum*) was characterized and identified from wheat in Ethiopia (O'Donnell et al. 2008). *Fusarium graminearum* and *F. pseudograminearum* were the FHB species identified in wheat fields in Western Australia (Tan et al. 2012; Obanor et al. 2013).

*Fusarium graminearum* is a pathogen of heightened concern for the wheat and barley industries due to its high pathogenicity and ability to cause severe disease under epidemic conditions (Xue et al. 2006, 2019). The species is evolving means to overcome host resistance genes, enabled by its mixed reproduction system, encompassing both sexual and asexual reproductive states, and allowing for genetic recombination and the propagation of clones (McDonald and Linde 2002). *Fusarium graminearum* is homothallic and thus does not require a compatible strain to produce perithecia (Cavinder et al. 2012). The genome of *F. graminearum* shows low levels of repetitive elements due to the targeting mechanisms associated with repeat induced point (RIP) mutation (Cuomo et al. 2007), thereby promoting rapid adaptation to selection pressures (Hane et al. 2015). *Fusarium* genome studies have demonstrated the existence of specialized pathogenicity chromosomes with evidence of horizontal acquisition (Ma et al. 2010). The pan-genomic analysis of North American isolates of *F. graminearum* has identified abundant signatures of selection within genomic regions of dispensable accessory genes associated with pathogen specialization (Kelly and Ward 2018). The extreme level of diversity and the significant correlation with genotypic variation in virulence that is observed within this pathogen for wheat and barley (Miedaner et al. 2001; Cumagun and Miedaner 2003; Garmendia et al. 2018; Sakr 2018) should be taken into consideration in development of breeding strategies.

Advancements in *Fusarium* genomics have elucidated the genes that the fungus uses for invasion, which may be host defence response elicitors. Cuomo et al. (2007) discovered high degrees of polymorphism in telomeric regions which contained an abundance of pathogenicity genes, and these genes are commonly expressed under host–pathogen interaction. The secretome of *F. graminearum* has been documented well (Brown et al. 2012; King et al. 2015), including over 600 proteins. The secreted proteins that function as cell wall-degradation enzymes (CWDEs) provide the fungus with an arsenal of virulence effectors to enter and colonize hosts. Biochemical characterization of the enzyme cocktail produced by *F. graminearum* in response to growth on media with a sole carbon source from glucose or hop cell wall material has demonstrated significant increases in the activities of the latter (5 vs. 17 CWDE activities) and enhanced ability to convert plant cell wall substrates into a variety of sugars (Phalip et al. 2009). The extracellular peptidases produced by *F. graminearum* during the infection of wheat and barley are highly similar ($r^2$ = 0.87), whereas the comparison of *in planta* vs. *in vitro* conditions demonstrates weak association ($r^2$ = 0.22), indicating host-induced pathways (Lowe et al. 2015). *Fusarium graminearum* strains of varying aggressiveness express the same genetic programmes and show similar effector protein profiles in wheat infections, but more aggressive strains accumulate these substances with higher abundance (Fabre et al.

2019), thus, aggressiveness is not determined by specific effectors, but rather by their general rate of production. The pathogen carries numerous pathogenicity factors that can be employed under various circumstances. The alternative ways this pathogen can invade a host may be responsible for the partial levels of resistance achieved in wheat and barley.

### *Trichothecene mycotoxin chemotypes and the population genetic structures of* Fusarium *species causing FHB in wheat and barley*

The population genetic structures of pathogenic fungi can provide insights into their evolutionary potential and could assist breeders in the development of FHB-resistant cultivars. Generally, four types of trichothecenes (A, B, C, and D) are produced in fungi. Types A and B are the trichothecenes produced by *Fusarium* spp. (Mirocha et al. 2003; Liddell 2003). The type B trichothecene group, made up of mainly DON and nivalenol (NIV), includes the main mycotoxins that accumulate in wheat and barley contaminated by *Fusarium* (Ward et al. 2002; Amarasinghe et al. 2019), and these mycotoxins are strictly monitored in flour-based, malting, and brewing industries since they are of major concern to feed and food safety (Tittlemier et al. 2013). Nivalenol producers have been documented within the USA and show the ability to dominate in some environments, e.g. southeastern USA, where a large population (79%) of 237 isolates of *F. graminearum* sensu stricto were of the NIV type (Gale et al. 2011). This is in sharp contrast with other regions of the USA, where the DON chemotype predominates in *F. graminearum* sensu stricto. Findings such as this are relevant in developing appropriate surveillance programs. In wheat and barley, NIV is mainly produced by *F. graminearum, F. culmorum*, and *F. cerealis* (Amarasinghe et al. 2015; Basler 2016). Reports have shown that the NIV chemotype may be influenced by host type. Strains producing NIV in both Europe and China have been found to be more aggressive in maize than other strains that produce DON (Carter et al. 2002; Ndoye et al. 2012). On the other hand, *Fusarium* spp. associated with DON production in wheat and barley include *F. graminearum, F. culmorum*, and *F. pseudograminearum* (Munkvold 2017). The DON chemotypes include isolates that produce the acetylated derivatives of DON, *i.e.* either 3-acetyl deoxynivalenol (3ADON) or 15-acetyl deoxynivalenol (15ADON) (Ward et al. 2002). The genetic basis of the chemotype, *i.e.* 3ADON vs. 15ADON, is controlled by the trichothecene biosynthetic gene *TRI8* (Alexander et al. 2011) in the *TRI* gene cluster, which encodes an esterase that differentially removes the acetyl group from the C-3 or C-15 position (McCormick and Alexander 2002). While 3ADON and 15ADON may possess different toxicities, these acetylated forms are commonly found at much lower levels than DON itself. As a sub-population characteristic, chemotype information is useful for investigating population dynamics.

In North America, the 3ADON chemotype population has been reported to be gradually replacing the 15ADON type within the last 20 to 30 years (Gale et al. 2007; Ward et al. 2008; Puri et al. 2016). Notably, 3ADON isolates have proven to be more aggressive and produce more DON than 15ADON isolates (Ward et al. 2008; Puri and Zhong 2010; Amarasinghe et al. 2015, 2019; Puri et al. 2016). The DON mycotoxin is regarded as a virulence factor, and having more isolates that produce 3ADON with respect to 15ADON is a serious concern in terms of mycotoxin contamination in plants and animals. This is because the change in the mycotoxin profile influences disease development in plants and translates into the contamination of grains utilized for animal feed and human food supplies. As toxins may act as virulence factors, the level of disease is also expected to rise under infection by pathogens with elevated toxigenic potential. Along with increased toxicity, other pathogenic characteristics are also associated with the 3ADON chemotype (such as fecundity and growth rate), implying a general increase in aggressiveness (Ward et al. 2008). The 3ADON forms are also more resilient, showing higher DON levels and faster mycelial growth in laboratory cultures following exposures to extreme heat and cold stresses (Vujanovic et al. 2012). The existence of more aggressive forms of pathogens imposes the necessity to select the isolates that best represent the pathogen population, also requiring continuous updating when screening breeding lines for resistance.

In Canada, the population genetic studies of province-wide collections of *F. graminearum* in wheat have revealed interesting temporal population dynamics. The 3ADON chemotype is more abundant in western Canada than eastern Canada, with no significant change during the period sampled when studied by Kelly et al. in 2015. Guo et al. (2008) reported a 95.7% prevalence of 3ADON in a population of 291 isolates of *F. graminearum* in wheat fields in Manitoba, Canada, from 2004 to 2005. In addition, using a sequence-related amplified polymorphism (SRAP) technique, they found no significant correlation between chemotype and cultivar type, but there was significant gene flow between subpopulations of geographic locations. These findings are similar to the results obtained by Fernando et al. (2006), who found significant gene flow between 60 *F. graminearum* isolates from

Carman and Winnipeg in Manitoba, Canada. Ward et al. (2008) documented a recent and dramatic shift in western Canada, where 3ADON chemotypes demonstrated a 14-fold increase in frequency between 1998 and 2004. In contrast, a survey of wheat fields in Ontario, Canada, from 2010 to 2012 indicated a 98% 15ADON population of 110 *F. graminearum* isolates, with generally high gene and genotypic diversity when observed via variable number tandem repeat (VNTR) markers (Burlakoti et al. 2017). Similar results were obtained in the Upper Midwest of the United States. A study of 463 *F. graminearum* strains revealed a temporal increase in the percentage of 3ADON isolates within the studied period spanning 11 years (Liang et al. 2014). Population genetic structure studies of 113 *F. graminearum* isolates in Argentina using amplified fragment length polymorphism (AFLP) markers found two populations that were genetically similar, with significant gene flow between the populations. These populations were thought to possibly be part of a larger population that allows random mating (Ramirez et al. 2006, 2007). Similar results for high gene flow were obtained by Talas et al. (2011) and Talas and McDonald (2015) when performing analyzes with simple sequence repeat (SSR) markers and single nucleotide polymorphisms (SNPs), respectively, where they analyzed 213 isolates of *F. graminearum* from the northern and southern parts of Germany. The high-gene flow observed in both studies suggests potential to create pathogen populations that can rapidly adapt to management strategies like fungicide applications and resistant cultivars. In contrast, population genetic studies of 712 *F. graminearum* isolates from the Upper Midwest of the USA showed the existence of significantly genetically different populations made up of both the 3ADON and 15ADON chemotypes, which might be due to insufficient recombination events between the two chemotype populations (Gale et al. 2007).

While the 3ADON chemotype is becoming predominant in North America, as described earlier, the situations are different in Germany, France, Italy, and England, where the 15ADON chemotype dominates wheat fields (Jennings et al. 2004; Talas et al. 2011; Boutigny et al. 2014; Somma et al. 2014). Evidence of a possible correlation between the 15ADON trichothecene chemotype of *F. graminearum* and host type has been suggested by several reports. *F. graminearum* is predominant in maize farms in several parts of the world. A 15ADON composition of >90% in maize fields has been reported in eastern Canada, several states in eastern USA, countries in Europe, and China (Schmale et al. 2011; Tamburic-Ilincic et al. 2015; Burlakoti et al. 2017; Hao et al. 2017; Bilska et al. 2018; Vogelgsang et al. 2019). As mentioned above, this trend has also been observed in wheat at these locations. Crippin et al. (2020) suggested that the dominance of 15ADON populations in wheat farms in Ontario is due to the stability of maize farms, coupled with the practice of minimum tillage, which increases the biomass proportion of overwintered ascocarps. These ascocarps can act as a primary inoculum in newly established wheat fields and can result in the establishment of further 15ADON populations. When comparing the genotypes and chemotypes of *F. graminearum* from maize and wheat samples from farms in Ontario, Crippin et al. (2019) confirmed that 15ADON is the predominant chemotype in eastern Canada and reported that 3ANX (15-deacetylcalonectrin) toxin production occurs concurrently with 15ADON. They also suggested that the 3ANX producers in North America probably originated from a 15ADON background.

In Asia, *F. asiaticum*, which is within the FGSC, is more common than *F. graminearum* sensu stricto in North America and Europe (Aoki et al. 2012). In Japan, a study of 183 FGSC isolates showed that 179 were identified as *F. asiaticum* and only four as *F. graminearum* sensu stricto. Chemotype analysis revealed 56% 3ADON, 44% NIV, and no 15ADON (Karugia et al. 2009). Findings from population genetic structure analysis in the same study using VNTR markers revealed a genetically similar population based on a low fixation index and high level of gene flow. Further proof of a shift to the more aggressive 3ADON isolates was investigated by Zhang et al. (2012) using VNTR markers for the assessment of 469 isolates of *F. asiaticum* and *F. graminearum* sensu stricto, covering 15 provinces in China. Additionally, the 3ADON isolates were more aggressive and showed higher levels of fungicide resistance. In China, VNTR marker analysis of 185 *Fusarium* isolates collected within a 28-year period resulted in a strong correlation between high-genetic diversity and mycotoxin production (Qiu et al. 2016). These results suggest natural selection as a dominant force in the introduction of more toxigenic pathogens into a region. Although there are few studies on the aerobiology of *Fusarium* pathogens, there is evidence of potential long-distance transmission for 3ADON genotypes into new regions (Schmale III et al. 2012).

The type A mycotoxins found in wheat include the very toxic T-2 toxin (T-2) and HT-2 toxin (HT-2) produced by *F. accuminatum, F. poae*, and *F. sporotrichioides* (Foroud and Eudes 2009; Foroud et al. 2019b). The T-2 toxin has been reported to be ten times more toxic in animals than

DON (Ueno 1983). A novel type A trichothecene, NX-2, produced through an altered *TRI1* gene and whose structure resembles the 3ADON chemotype, was discovered in low frequencies in wheat in Canada and in the northern USA (Liang et al. 2014; Kelly et al. 2015, 2016). Indicators of selection pressure exist for genomic divergence at the trichothecene toxin gene cluster, where variations in toxigenesis may contribute to increased virulence (Kelly and Ward 2018). The NX-2 trichothecene mycotoxin is similar in toxicity to 3ADON isolates, but its deacetylated form (NX-3) is ten times more toxic than NX-2 (Varga et al. 2015). A collection of 4117 isolates of the FGSC from eight provinces of Canada from 2005 to 2007 revealed 12 isolates with the NX-2 chemotype (Kelly et al. 2015), and 2.8% NX-2 isolates were obtained from 463 isolates of *F. graminearum* in the Upper Midwest of the USA (Liang et al. 2014). Lofgren et al. (2018) investigated a subset of previously identified 3ADON-producing *F. graminearum* isolates in the USA. They reported that previous studies might have incorrectly identified NX-2 populations as 3ADON due to the similarity in the chemical structures of both chemotypes. Therefore, the possibility exists that NX-2 populations in *Fusarium* species in wheat in North America may be more common than as previously reported.

## Epidemiology

*Fusarium graminearum* belongs to the Ascomycota, a phylum characterized by the formation of an ascus or sac where sexual spores develop. *Fusarium* pathogens that cause FHB in wheat and barley can infect kernels, spikelets, or the full head, making them appear water-soaked as they lose chlorophyll and become bleached (wheat) or grey-brown (barley). The infection can spread to other spikes or can move along the entire head, as seen in wheat. Infective bodies are primarily derived from the infected residues of preceding crops (Dill-Macky and Jones 2000) and/or non-crop grass species (Turkington et al. 2011). Infection is initiated by the release of sexual spores (ascospores) from the perithecial bodies that develop on crop residues and are carried to host spikes via wind. Ascospores are released 2–4 days after major rainfall events in a diurnal fashion, starting in the afternoon with the peak achieved by midnight (Paulitz 1996; Fernando et al. 2000; Inch et al. 2005). Airborne ascospores are the primary inoculum source, and the disease is generally characterized as monocyclic in the Canadian environment due to the absence of a secondary inoculum, as observed from disease gradient slopes (Fernando et al. 1997). To a lesser extent, infection can occur as the result of the splash dispersion of asexually produced spores (macroconidia), either directly from crop residues or via secondary infections arising from primary infection sites. While *F. graminearum* can infect non-spike tissues and is one of several *Fusaria* commonly associated with crown rot, the fungus is not capable of systemic growth from the crown to the spike (Xi et al. 2008; Moretti et al. 2014). Following contact with the host spike, ascospores and/or macroconidia germinate, where germ tubes differentiate to hyphae. These spores have been observed to germinate very quickly within 6–12 h for wheat (Pritsch et al. 2000), but with a longer period of 24 h for barley (Boddu et al. 2006). *Fusarium graminearum* also displays a longer period from colonization to the onset of pathogenicity-related gene expression in barley (Lysøe et al. 2011) and relatively lower gene expression overall for this host (Harris et al. 2016). In relation to other *Fusarium* species, *F. graminearum* displays an elevated propensity to form an expansive hyphal network, particularly in warm and humid conditions (Bushnell et al. 2003). Hyphal networks are established to explore the host surface in response to stimuli associated with accumulating nutrients. Hyphal growth on exterior surfaces is considered to be an important opportunistic step in the infection process, which allows the pathogen to discover stomata or other entry points.

Anthesis is a period of high susceptibility of the host to the fungus, and this period is particularly notable for wheat. The optimal conditions for host infection at anthesis may differ between wheat and barley, where the latter shows moderate temperatures (15°C) are favourable to severity (Schöneberg et al. 2018) vs. warmer temperatures for wheat (> 20°C) (Osborne and Stein 2007). Flowering in wheat is associated with the swelling of the lodicules that open the floret, making the host vulnerable to infection. While florets are temporarily open, airborne spores may directly land inside the floret or hyphae and may grow into the inner cavity. This vulnerability is prolonged further by any dehisced anthers that are caught between closed lemma and palea, allowing extended access to hyphae. Senescing anthers are also a stimulant for fungal colonization (Strange and Smith 1971; Strange et al. 1974). The formation of choline and betaine by wheat during anthesis is an important factor in the interaction of wheat and *F. graminearum*. These two constituents have been reported as growth stimulants for *F. graminearum*, and thus their accumulation in wheat anthers is considered as a susceptibility factor (Strange

et al., 1974). As shown by Brand and Gow (2012), an ideal hyphal orientation is essential for successful infection. When assessed under experimental conditions, the growth of *F. graminearum* conidia after germination was observed to be directed to the ovary (Blumke et al. 2014). While hyphal chemotropism towards nutrients is a generally accepted event, the underlying mechanisms are still not completely understood (Turrà et al. 2015).

A study of visual symptom data collected in a time course infection experiment on wheat found that the fungal biomass was correlated with anthesis, but not after anthesis (Beccari et al. 2020). Consequently, visual symptoms of FHB after anthesis might be a poor estimator of infection levels in wheat kernels. Infection at a single point on a wheat spike spreads along the spike, but the exact nature of the nutritive mode of *F. graminearum* is still unclear. While open flowered barley cultivars exist, closed flower varieties are more common in Canada. The pollination of barley commonly occurs while the spike is in the boot, thereby providing a physical barrier of protection during this developmental stage. Once spikes emerge, the lignified thick-walled epidermal cells of the abaxial surfaces of the lemma and palea offer defence to direct penetration. However, the pathogen can gain access to the floret interior through the floret mouth or via the overlapping regions of lemma and palea (Lewandowski et al. 2006). Once inside the floral cavity, the fungus has a high probability for completing the infection process. The adaxial surface of lemma and palea has a thin epidermis that is more easily penetrated by infection pegs. Likewise, as revealed by the use of a strain transformed by a green fluorescent protein gene (gfp), brush hairs (ovary epithelial hairs) of barley have been shown to be a target for colonization (Skadsen and Hohn 2004). *Fusarium graminearum* has an arsenal of cell wall-degrading enzymes at its disposal to facilitate this process. The fungal hyphae differentiate into specialized infection structures, such as foot structures or compound appressoria, e.g. lobate appressoria or infection cushions (Jansen et al. 2005; Boenisch and Schäfer 2011; Qiu et al. 2019a). The fungus lives for a short biotrophic period within the apoplast for a few days, during which it does not appear to cause harm to the host.

Following the brief initial biotrophic period, the pathogen alters its approach to a necrotrophic nature. At approximately 72 h post-infection, a dramatic increase in DON is observed in barley (Evans et al. 2000; Boddu et al. 2006). The increase in mycotoxins at this stage is associated with increased fungus proliferation and intracellular growth. It is well documented that DON is a virulence factor for wheat and is required for the fungus to bypass the barrier imposed by the rachis and spread throughout the spike via the vascular tissues (Jansen et al. 2005). Barley differs from wheat in this regard, demonstrating effective type II resistance (Mesterhazy 1995), even in susceptible varieties. Beyond the path through the rachis, under conditions of high humidity, hyphae may grow on the outside of the spike surface to reach and infect distal florets. Stomata or injury points may also provide the fungus with alternative stochastic entry routes. Silica cells associated with trichomes of lemma and palea can be directly penetrated and may also be vulnerable to later infection in barley (Imboden et al. 2018). *Fusarium* infection in barley can occur over a two-week period following heading, where this extended period can increase the chances of exposure to events with favourable infection conditions (McCallum and Tekauz 2002). While open flowering barley is susceptible during anthesis, as with wheat, closed flowering barley demonstrates increased susceptibility at later stages (Yoshida et al. 2007, 2008). The expression of FHB in wheat and barley is quite different, where FHB in wheat often appears as the bleaching of significant portions of the spike and results in chalk-like tombstone kernels in more severe infections. In barley, the infection of kernels is more individualized and is observed with the browning of florets. At maturity, *Fusarium*-damaged kernels can be more difficult to distinguish in barley, which can be characterized as slightly shrivelled and stained (Fig. 1). The epidemiology of FHB is affected by cultural practices such as tillage, the previous crop used in rotation, and the genetic characteristics of the given cultivar (Champeil et al. 2004; Gilbert and Fernando 2004).

### *Resistance to DON*

While DON is produced at low concentrations in the early phases of infection, at 72 h post-infection, the DON content quickly rises in barley spikes and is associated with a lifestyle switch from biotrophy to necrotrophy (Boddu 2006). The DON mycotoxin has been identified as a virulence factor in barley, where wild-type cultures have been shown to produce higher disease severity in spikes when contrasted with *TRI5* gene loss-of-function mutants (Boddu et al. 2007). Deoxynivalenol inhibits protein synthesis (Desjardins 2006) through binding to the 60S subunit of the eukaryotic ribosome inside the peptidyl transferase centre (Garreau de Loubresse et al. 2014), thereby interfering with the translation of messenger RNA. Given the essential activities of the ribosome, its components are highly conserved, thus making it easily targeted by pathogens (Foroud et


**Fig. 1** **(a)** Wheat heads with symptoms of Fusarium head blight (FHB) showing characteristic bleached spikelets. **(b)** Wheat head showing both infected and non-infected spikelets. **(c)** Fusarium damaged wheat kernels (left) and healthy wheat kernels (right). **(d)** Barley heads infected in the field showing a premature brownish discolouration of spikelets characteristic of FHB. **(e)** Harvested barley heads with FHB symptoms. **(f)** Barley seeds of different cultivars showing mild to severe FHB symptoms: (i) moderately resistant – MR, (ii) moderately resistant, moderately susceptible – MRMS, and (iii) susceptible – S.

al. 2019b). Through disruption of the translation process, the pathogen sequentially interferes with potential protein-driven host defence mechanisms. Programmed cell death (PCD) is an induced mechanism used to halt pathogen spread. In a cell culture system study of the model plant species *Arabidopsis thaliana*, DON showed the ability to inhibit and disarm the apoptosis-like PCD response that is typical of hypersensitive response-induced defence (Diamond et al. 2013). While DON is not required for *F. graminearum* to infect its host tissues, specialized infection structures are associated with the production of DON, albeit at low levels (Boenisch and Schäfer 2011). Early production of DON during the biotrophic phase may be associated with the suppression of plant defence mechanisms, representing the first phase of DON–host interaction.

Deoxynivalenol is a secondary metabolite produced by *F. graminearum*, acting as a multifaceted stress responder when encountering various conditions in the environment. These conditions can be physical in nature or biological under interaction with antagonistic microorganisms during the saprophytic phase or with the host during host infection (Audenaert et al. 2013). DON production is induced in *F. graminearum* by several stimuli, including a low pH (Gardiner et al. 2009a; Merhej et al. 2010), sugars (Jiao et al. 2008), and arginine-polyamine pathway products (Gardiner et al. 2009b, 2010). DON is also prompted in response to conditions of oxidative stress associated with hydrogen peroxide ($H_2O_2$), which is commonly produced as an early plant defence response (Ponts et al. 2006, 2007; Ponts 2015). In *F. graminearum*, the reactive oxygen species (ROS) equilibrium is tightly controlled, where a loss of virulence is observed in mitogen-activated protein kinase gene *FgOS-2*-deficient mutants through the downstream impact on the Activating transcription factors/cAMP response element binding protein (ATF/CREB) transcription factor *Atf1* (Nguyen et al. 2012, 2013). Using a sensitive fluorescent indicator protein (HyPer-2), Mentges and Bormann (2015) demonstrated the elevation of intracellular $H_2O_2$ in the specialized infection cushions of *F. graminearum* via confocal laser scanning microscopy, implicating its role in early host–pathogen interaction. The fungus stimulates a host-stress response and then uses this as an opportunity to trigger further DON production, creating a positive feedback cycle. Further increases in DON promote plant defence mechanisms and an increased oxidative state, resulting in damage to the cellular components of the plant. In this sense, DON acts as an effector, where it elicits plant host defences which eventually lead to cell death (Desmond et al. 2008). Elevations in DON prepare cells for the next phase of necrotrophic infection following movement from the apoplast to intracellular space, where nutrients are derived by killing cells and consuming dead tissues.

### *DON conjugation*

The molecular mechanisms that slow the spread of Fusarium within the barley heads have been well characterized. Previous gene expression studies involving a ± *TRI5 F. graminearum* challenge (Boddu et al. 2007) or topical DON application (Gardiner et al. 2010) have documented strong upregulation for DON-specific resistance in barley. A predominant defence is achieved through the conjugation of DON with a glucose molecule to form D3G. This is achieved through resistance response enzymes such as uridine diphosphate (UDP) glucosyltransferases (UGTs). Four barley UGT genes were functionally characterized through heterologous expression in yeast, where only *HvUGT13248* (*MLOC_65675; HORVU5Hr1G047150*) demonstrated DON resistance (Schweiger et al. 2010). The function of *HvUGT13248* in DON resistance has been further evaluated through the transformation of *A. thaliana* (Shin et al. 2012) and wheat (Li et al. 2015). Using transgenic wheat, the function of this gene has been further characterized to confer resistance and convert NIV to the less toxic form of nivalenol-3-glucoside (N3G), with even greater efficiency than DON (Li

et al. 2017). The virus-induced gene silencing of an ABA receptor, *Ta_PYL4AS_A*, in *F. graminearum* produced plants with an increased early state for FHB type II resistance and decreased mycotoxin contamination, suggesting a potential target for further resistance studies (Gordon et al. 2016).

### *Restriction of DON biosynthesis*

A series of metabolic profiling studies have been conducted in cereals to identify *F. graminearum* or *F. culmorum* resistance-related metabolites through the application of mass spectrometry (e.g. as reviewed by Gauthier et al. 2015). Several studies of barley have repeatedly detected significant fold changes in specific metabolite groups that are in contrast, involving resistant genotypes to susceptible control(s) (Bollina et al. 2010; Eggert et al. 2010; Bollina et al. 2011; Kumaraswamy et al. 2011a, 2011b; Kumaraswamy 2012; Cajka et al. 2014; Chamarthi et al. 2014). The detected chemical groups represented as resistance-related metabolites were the following: flavonoid phenylpropanoids, non-flavonoid phenylpropanoids, fatty acids (jasmonic acid, linolenic acid), terpenoids, hydroxycinnamic acid amides, and alkaloids. The most commonly induced metabolite group is flavonoids (Gauthier et al. 2015). Flavonoids have strong antioxidative properties, resulting in production reduction and the quenching of ROS through several mechanisms (Mierziak et al. 2014). Reductions in oxidative stress are hypothesized to result in negative feedback for trichothecene production (Ponts et al. 2006, 2007; Ponts 2015). As trichothecene metabolism is dependent on the presence of molecular oxygen to complete several reaction steps, the presence of antioxidative compounds may also inhibit their synthesis. Boutigny et al. (2008) provided a review on the role of phenolics as antioxidant compounds on inhibition of mycotoxin formation.

Studies identifying associated compounds have led researchers to investigate these compounds further. The properties of resistance-related metabolites have been examined through assays directed to evaluate the activities regarding the inhibition of mycelial growth or trichothecene production. Bollina and Kushalappa (2011) evaluated 10 selected molecules from phenolic, flavonoid and fatty acid chemical groups, demonstrating complete trichothecene inhibition by the lauric, p-coumaric, sinapic, and ferulic acids, as well as naringenin, quercetin and methyl jasmonate. In both spring and winter wheat samples, phenolic acids, lutein, and β-carotene were found to reduce DON accumulation (Etzerodt et al. 2016). The identification of metabolites that effectively reduce DON production could be pursued through the development of convenient assays for plant breeders to use as biomarkers. The manifestation of compounds in specific tissues may be of importance. For example, through the use of mutants, Skadhauge et al. (1997) demonstrated the importance of proanthocyanidins in the testa layer, which prevented the further penetration of hyphae by *F. culmorum* in barley seeds. Resistance strategies that rely on limiting the initial production of toxins vs. detoxification, such as glycosylation, may be preferred as conjugated toxins are readily converted back to their more toxic form in the mammalian gut.

## Host

### *Breeding for FHB resistance and germplasm development*

There are several types of FHB resistance which breeders can apply for selection, including: type I, resistance to initial infection; type II, resistance to spread from the point of infection; type III, resistance to kernel infection; type IV, tolerance to FHB yield loss; type V, resistance to DON accumulation; and type VI, resistance to the modification of grain constituents (Mesterhazy 1995; Martin et al. 2018).

### *Fusarium head blight candidate disease resistance genes and breeding strategies in wheat*

Generally, plant resistance to a pathogen attack can either be qualitative or quantitative. Qualitative plant resistance results in discrete classes of phenotypes that correspond to simple Mendelian ratios which result in a single genetic locus when mapped, while quantitative resistance produce a continuous distribution of phenotypes that map to a number of genomic loci (Corwin and Kliebenstein 2017). Quantitative resistance controls the vast majority of host–pathogen interactions. As described above, FHB resistance has been classified into two main types, *i.e.* type I resistance and type II resistance (Schroeder and Christensen 1963). Host resistance in wheat against FHB has been studied exhaustively and is mostly quantitative in nature (Brar et al. 2019a). The quantitative nature of the resistance in wheat makes breeding quite a difficult task, especially when only conventional breeding methods are used. Effective disease-resistance genes should be durable. The FHB-resistant Chinese wheat cultivar ‘Sumai 3′, discovered in 1970, has been used extensively as a source for resistance in wheat breeding programs

across the world (Niwa et al. 2014). Several FHB-resistant genes derived from Sumai 3 which exhibit resistance in wheat include *Fhb1, Fhb2*, and *Fhb5* (Cuthbert et al. 2006, 2007; Xue et al. 2011). Molecular markers for *Fhb1*, which has been cloned, are abundant and are being used in breeding programs worldwide (Ma et al. 2019). An example is the diagnostic marker UMN10, which is widely used for the verification of resistant QTL in wheat (Liu et al. 2008). The main aim of breeders is to transfer resistance to FHB into lines with desirable quality and agronomic characters. Marker-assisted-selection (MAS) is chosen over conventional breeding because of its speed, simplicity, and ability to pyramid both minor and major genes (Haber et al. 2008).

MAS is a breeding process where a marker (morphological, bio-chemical or genetic) is used to indirectly select for a desirable trait through linkage to the marker. The genetic background and epistatic interactions play major roles in improving resistance in 'Sumai 3′ derivatives in the MAS of hexaploid wheat (Brar et al. 2019a). Difficulties in maintaining desirable agronomic qualities during the introgression of FHB resistance have led some breeders to try out some unconventional breeding methods. Acceptable levels of disease resistance can be achieved through the MAS of lines developed by the introgression of these genes, but challenges related to reduced grain protein contents (GPCs) arise as a result (Brar et al. 2019b). The high GPC gene *Gpc-B1* was utilized in MAS to develop wheat varieties with high GPCs without compromising yield, as reviewed by Balyan et al. (2013). The relative successes of these breeding efforts have been possible due to germplasm exchange between Asia and North America. Field responses of 'Sumai 3′ derivatives to FHB infection can vary widely due to genetic diversity. It is thus advisable to replace a susceptible allele with a resistant one in the crossing parents (Niwa et al. 2014).

Recently, Wang et al. (2020) reported the molecular identity of another gene (*Fhb7*). This gene encodes a glutathione *S*-transferase that detoxifies DON, conferring semi-dominant resistance. It was shown that it was acquired through a 'natural' fungus-to-plant gene transfer from *Epichloë*, a widely distributed ascomycete fungal genus that colonizes many grasses, to the wild wheat grass relative *Thinopyrum ponticum*. The new in-depth knowledge for *Fhb7*, along with the genes reported earlier, provides breeders with the opportunity for gene pyramiding, which might confer optimal control for FHB in wheat. Also, the engineering of *Fhb7* in order to increase resistance to FHB in other cereals (such as barley and rye) or crown rot in wheat and ear rot in maize can now be considered (Wulff and Jones 2020).

Before the onset of next-generation sequencing and advanced bioinformatics annotation tools, candidate disease-resistance genes of FHB in wheat were studied using expressed sequence tag (EST) markers. The cloning of ESTs mapped to a region on the short arm of chromosome 3B, which contains QTL that contribute to FHB resistance, revealed a leucine rich EST that could be used as a potential marker for resistance screening (Shen et al. 2006). Targeting important pathogenicity factors utilized by *Fusarium* pathogens during infection in wheat is a developing research area that can be exploited to produce FHB-resistant cereals. Likewise, a similar study using RNA interference (RNAi) for the host-induced gene silencing (HIGS) of the benzoxazinoid detoxification gene *NAT1* in *F. graminearum* in several wheat cultivars reduced the DON content (Baldwin et al. 2019). Host-induced suppression is a non-transgenic approach that shows potential for use in targeting multiple host genes to develop resistant varieties. Transcriptomic and effectoromic approaches are important tools that play significant roles in the identification of durable and sustainable defence genes for FHB resistance (Piquerezt et al. 2014).

Recently, Bhatta et al. (2019) screened 125 lines of hexaploid wheat and identified 124 marker trait associations and 33 potential candidate genes with multiple resistance against stem, leaf, and stripe rusts of wheat. Genome-wide association studies of FHB resistance in wheat are common in the literature. These studies have greatly facilitated variety development for FHB resistance in wheat using MAS. The international institutions at the forefront of using GWAS in developing FHB-resistant lines are the International Maize and Wheat Improvement Centre (CIMMYT) and the International Centre for Agricultural Research in the Dry Areas (ICARDA). These two institutions have a large reservoir of wheat lines that have been screened for resistance to major wheat diseases, including FHB. The main objective at CIMMYT is to increase the productivity of wheat varieties to reduce poverty in developing countries (Guzman et al. 2016). Achievements are facilitated by the chromosome-based draft sequence data for the hexaploid bread wheat (*Triticum aestivum*) genome, which were made available by the International Wheat Genome Sequencing Consortium (IWGSC) in 2014. Genome-wide association mapping of a panel of CIMMYT spring wheat lines has revealed 14 lines with resistance to FHB in different environments (Wang et al. 2018c). The promising aspect of these lines is the fact that Sumai 3 was

absent in the background of this panel. The eight predicted proteins from the SNP analysis of GWAS studies of a panel of spring wheat from the mid-western and eastern United States associated with FHB resistance are important as a resource for functional characterization (Arruda et al. 2016a). Simultaneous screening of a particular agronomic character, together with FHB resistance, can also be achieved in breeding programs. In Japan, hard red winter wheat lines were screened using more than 1000 microsatellite (SSR) markers, which resulted in the identification of two FHB-resistant QTL closely linked with genes for low gluten content (Nishio et al. 2016). Various associated agronomic character and FHB resistance studies have been carried out at CIMMYT. Anther extrusion (AE) was shown to be closely related with FHB in field breeding trials of CIMMYT recombinant inbred lines (RILs) based on five QTL that were associated with both traits (Xu et al. 2020). Lines from the wheat-breeding programs at CIMMYT have been sent for phenotyping to multiple countries (Mexico, Norway, Uruguay, Netherlands, Japan, and Canada), resulting in elite FHB lines with novel resistance QTL without a 'Sumai 3′ background (Osman et al. 2015). FHB-resistant QTL can be introgressed between different wheat types. A major breakthrough has been the successful transfer of a major FHB resistance QTL for hexaploid wheat into durum wheat, as tested in both greenhouse and field trials (ZZhao et al. 2018).

Durum wheat or 'pasta wheat' (*Triticum durum* Desf.) (AABB tetraploid) is known to be very susceptible to FHB, mainly due to the very limited genetic variation of cultivars available within these species. The equally important pasta industry, in comparison with bread, has led to major interests in breeding for FHB resistance with durum wheat. Introgression breeding strategies have proven very useful in these efforts. The introgression of *Fhb1* from 'Sumai 3′ into durum wheat was achieved for the first time by evaluating RILs, which revealed *Rht-B1*, which also governs plant height as a strong marker for FHB screening in durum wheat (Prat et al. 2017). Similar possibilities for the potential transfer through introgression from *Thinopyrum elongatum* to wheat have been reported. Disease resistance genes on chromosome 7E of *Thinopyrum elongatum*, a close relative of wheat, include potential resistance QTL that can be introgressed to wheat to create wheat lines with resistance to FHB and rusts (Chen et al. 2013). A similar study using the sister species *Thinopyrum junceiforme* produced amphiploid lines (13 G819) resistant to FHB which could be integrated into FHB-resistant wheat breeding programs (Li et al. 2019). The main focus of wheat breeders is to create lines with primarily type II FHB resistance, which stops the spread of symptoms along wheat spikes. Recently, the construction of a genetic map from inbred breeding lines of 'Yangmai 158′ from China indicated a novel quantitative trait locus (*QFhb-5a*) associated with type II FHB resistance in wheat (Jiang et al. 2020). This QTL has been proposed as an excellent region for FHB-resistant wheat breeding programs. Breeding for resistance to multiple wheat diseases is a major goal in crop breeding. A reservoir of suitable germplasm is an important resource in terms of parents in future breeding efforts. Spring wheat lines containing the major and well-characterized resistance QTL *Fhb1* and *Sr2* for FHB and stem rust resistance, respectively, have been developed from a wide collection of populations using tightly linked DNA markers (Zhang et al. 2016).

In Canada, breeding for FHB resistance in spring wheat started by utilizing resistance QTL from the Brazilian cultivar 'Frontana'. This resulted in one of the earliest FHB-resistant Canadian western red spring wheat (CWRS) cultivars, 'Neepawa', which is grown on the Prairies (*i.e.* the provinces of Alberta, Saskatchewan, and Manitoba) and accounted for 90% of the production of Canadian spring wheat (Gilbert and Tekauz 2000). Subsequently, some breeding programs have utilized cultivars from North Dakota (Mergoum et al. 2005) to transfer FHB resistance from 'Sumai 3′ into what is regarded now as the top three spring wheat cultivars: 'AAC Brandon', 'AAC Elie', and 'Cardale', respectively (Zhu et al. 2019). These cultivars, together with the hard red spring cultivar 'AC Barrie', are grown extensively on the Canadian Prairies. Mapping of the QTL in 'AC Barrie' was carried out recently (Thambugala et al. 2020). Notably, the spring red wheat 'AAC Tenacious' is currently the only Canadian spring wheat cultivar with a 'resistant' rating to FHB (Brown et al. 2015), and the major QTL of this cultivar have recently been mapped (Dhariwal et al. 2020). Breeding programs for FHB resistance in winter wheat have produced the cultivars 'AC Morley' and 'Emerson', which are used extensively in the province of Ontario, Canada, and which represent the majority of winter wheat in eastern Canada (Kang-Choi et al. 2016).

'Emerson' is the first wheat cultivar of any class in western Canada rated as 'resistant' to FHB. It was reported previously that the parents of 'Emerson' lack the commonly employed FHB QTL (Badea et al. 2008). This, coupled with the transgressive segregation from both parents, suggests that the low FHB levels in

'Emerson' could result from a unique gene grouping/interaction that involves uncharacterized sources of resistance (Graf et al. 2013). New research work has been prompted in regards to the evaluation of the genetics and cultural practices for FHB control (Ye et al. 2017), the development of a high-density map to identify QTL for FHB resistance (Kang-Choi et al. 2016), and the pyramiding of multiple FHB resistance QTL (Zhu et al. 2019), using 'Emerson' as the source plant material.

In the United States, the winter wheat cultivar 'NC-Neuse' was screened to provide three QTL markers (*Qfhb.nc-1A, Qfhb.nc-1B*, and *Qfhb.nc-6A*) with strong potential for use in MAS for FHB-resistant winter wheat lines (Petersen et al. 2016). In China, a novel quantitative trait locus (*QFhb.cau-7DL*) comparable to *Fhb1* in 'Sumai 3′ in terms of the magnitude of resistance was detected on chromosome arm 7DL (Ren et al. 2019). The validated comparison with *Fhb1* makes this a potential marker for use in FHB resistance breeding. Currently, the registration of a new Canadian winter wheat variety requires a rating for FHB resistance of at least 'moderately susceptible' (Laroche et al. 2019), which most likely will be raised to 'intermediate resistance' in the coming years. Gene pyramiding also has yielded very promising results in wheat breeding. Native FHB-resistance genes from local winter wheat varieties in the USA have been introduced through the application of identity-by-descent-based (IDB-based) linkage mapping into the winter wheat cultivar 'Wesley' with the *Fhb1* background (Eckard et al. 2015a). Similar approaches taken to introduce native resistance into spring wheat have resulted in identification of a novel QTL on chromosome 2A (Eckard et al. 2015b). Isolation of FHB-resistance genes via *Fhb1* and use of the derived markers for screening multiple wheat accessions requires a continuous breeding effort. A pore-forming toxin-like (PFT) gene on *Fhb1* is a promising marker for breeding wheat varieties (He et al. 2018). The mapping of QTL in wheat has been reviewed extensively recently (Buerstmayr et al. 2019; Zhu et al. 2019; Ma et al. 2020). Recent advances provide optimism towards achieving suitable resistance in wheat cultivars against FHB, but a lot of work still lies ahead.

### *Barley-breeding strategies*

In barley, the breeding programs have used several main approaches similar to those used in wheat for the development of FHB-resistant germplasm and cultivars, including the introgression of resistance from unadapted germplasm or from elite breeding lines used as bridging parents, and also transgressive segregation and *in vitro* selection.

The identification of FHB-resistant barley has been a long-term process, which has involved the screening of tens-of-thousands of gene bank accessions through various methods by numerous research groups from across the world. In the USA, screening efforts were conducted in the late 1920s in response to epidemics at that time, where several moderately resistant accessions were identified. The Swiss landrace Chevron (CIho 1111) was identified to have both stem rust (*Puccinia graminis* f. sp. *tritici*) resistance (*Rpg1*) and moderate FHB resistance (Shands 1939). This line has proven to be one of the most-resistant six-row accessions ever identified and has been a foundational source for breeding FHB resistance. The American six-row variety 'MNBrite', with Chevron in its ancestry, carries moderate FHB resistance developed through indirect selection for kernel brightness. Kernel staining is associated with a complex of pathogens, including *Fusarium* species (Rasmusson et al. 1999). The resistance of 'MNBrite' was further combined with the Chinese two-row accession variety 'Zhedar 2′ to develop 'Quest' (PI 663 183), which is a moderately resistant six-row variety with suitable malting quality (Smith et al. 2013).

Regular and severe epidemics have become common in eastern Asian countries (Choo 2009), where significant efforts in evaluating germplasm to identify resistance sources for barley occurred in the previous century. In Japan, several studies were carried out to identify resistant germplasm (Ikeda et al. 1955; Heta and Hiura 1963; Gocho and Hirai 1987; Takeda and Heta 1989; Takeda and Wu 1996). Likewise, significant screening efforts were performed in China (Chen et al. 1982, 1991; Zhou et al. 1991). Following epidemics in the mid 1990s, revitalized screening efforts were conducted in North America, including in the USA (Prom et al. 1997; Scholz et al. 1999; Steffenson and Scholz 2001; Skoglund and Menert 2002), Canada (McCallum et al. 2004; Tucker et al. 2009), and Mexico (Gilchrist 2001; Gilchrist et al. 2001). Evaluation of germplasm has also been conducted in Europe (Buerstmayr et al. 2004; Vančo et al. 2007). Many of the accessions identified earlier in eastern Asia have been validated in the North American growing environment, but poor-malting qualities (Urrea et al. 2005) and unadapted natures due to photoperiod sensitivity have posed some problems in their utility for breeding (Franckowiak 2001). Huang et al. (2013) studied a panel of 78 moderately resistant accessions using 1727 diversity array technology (DArT)

markers, where population structure analysis indicated clustering within spike types and growth habits and broad diversity within groups. Haplotype analysis of genomic positions associated with FHB QTL (2 H bins 8, 10, 13 and 6 H bin 7) has also been conducted, with a few accessions with distinct haplotypes have been identified. From the immense collective efforts by researchers over the globe over the past decades (collectively more than 30 000 accessions), little more than a 100 lines have been identified with moderate resistance, where a notable immune response has not been identified (Steffenson et al. 2003, 2016).

In the 1980s, more frequent isolation of *F. graminearum* and its associated mycotoxins was first observed from wheat samples originating in the Red River Valley region of western Canada (Clear and Abramson 1986; Abramson et al. 1987; Clear and Patrick 1990). While not initially regarded as a problem for other cereals, *F. graminearum* soon adapted to the barley crops in the region (Tekauz et al. 2000). In a couple of years, observations of infected barley increased from a sporadic incidence to detection in nearly all fields surveyed within Manitoba (Clear et al. 1996, 2000; McCallum et al. 2000). Since it was originally observed in eastern Manitoba, FHB has spread progressively to barley growing regions further west (Turkington et al. 2002), such that the situation in Canada is currently dire. Crosses were initiated in 1996 in the two-row malting barley-breeding programme at the Agriculture and Agri-Food Canada, Brandon Research and Development Centre (AAFC-Brandon). Over 50 resistance sources have been used within this program; however, very few breeding lines were advanced to the registration testing level in the early 2000s (Legge et al. 2004). Some of the mentionable exotic resistance sources that have resulted in successful crosses include 'Harbin' (China) and 'Svanhals' (Sweden). More recently, the crosses made with the Harbin-derived elite breeding line TR04282 (Harbin/TR253//TR253) have resulted in the release of two moderately resistant two-row malting barley cultivars that also incorporate resistance to other diseases of economic importance and have attractive malting profiles: 'AAC Connect' (Legge et al. 2017) and 'AAC Goldman' (Legge et al. 2018). The FHB breeding efforts at the Field Crop Development Centre, Alberta Agriculture and Forestry (FCDC-AAF), have also focused on the development of multi-disease resistance through partnership with ICARDA/CIMMYT (He et al. 2015; Osman et al. 2019). Breeding for FHB resistance in eastern Canada has focused on 'Chevron' and 'Quest' resistance within the six-row breeding program (R. Khanal, personal communication) and has also used 'Mimai 114′ (origin, China) to develop the two-row hulless cultivar 'AC Alberte' (Choo et al. 2001). Breeding with exotic cultivars has generally been difficult, requiring multiple breeding cycles with back-crossing to create sufficient elite germplasm to achieve progeny with acceptable agronomics, and in particular, acceptable malting quality.

While breeding efforts with exotic barley germplasm may provide resistance alleles that are uncommon in the Canadian gene pools, the identification of resistance within adapted cultivars has also provided heritable variation for developing resistant cultivars. Two-row barley is generally more resistant than six-row barley (Choo et al. 2004), and the founder genetics of Canadian germplasm such as the two-row cultivars 'Harrington' and 'AC Oxbow' have contributed to the general resistance levels of modern cultivars (Tekauz et al. 2000; Rudd et al. 2001). Known resistance sources such as 'Svanhals' and 'Chevron' (via 'Chevron' selection with 'Peatland') are present in the pedigrees of Canadian founder lines, which may have conferred resistance alleles amongst others inherently carried within European-based breeding pools. As in wheat, transgressive segregation for resistance has also been observed in barley (Zhu et al. 1999). The ability to combine resistance is an important factor that should continue to be exploited when breeding for FHB resistance. 'Island', a moderately resistant general-purpose cultivar developed in eastern Canada, also has a European resistance foundation (Choo 2006). 'Conlon', an American two-row cultivar released by North Dakota State University, was not bred specifically for FHB resistance, yet demonstrates moderate resistance. Complementary crosses between elite Canadian breeding lines have resulted in progeny with superior resistance than their parents and the development of moderately resistant cultivars adapted to western Canada, such as 'CDC Mindon', developed at University of Saskatchewan's Crop Development Centre (Rossnagel et al. 2008), and 'Lowe', developed at FCDC-AAF (Juskiw et al. 2019). It is possible that, through the creation of complementary crosses, further improvements in resistance may be achieved through matching additive effects and/or possible epistatic contributions.

Another method used for the development of FHB-resistant wheat and barley is *in vitro* selection (IVS) (Foroughi-Wehr and Wenzel 1990; Fadel and Wenzel 1993; Lu et al. 1998; Eudes et al. 2007). FHB-resistant somaclonal lines have been released as cultivars in both wheat (Lu et al. 2001, 2003) and barley (Choo et al.

2000). IVS seems to be particularly efficient when paired with a doubled haploid system, which fixes alleles by removing heterozygous conditions under a single generation. An anther co-culture assay for the regeneration of doubled haploids under media with trichothecenes has been used to develop FHB-resistant wheat lines (Eudes et al. 2008). A similar approach was taken with AAFC-Brandon for IVS application using mycotoxins in an anther culture system. 'Norman' (Legge et al. 2011), a doubled-haploid two-row malting cultivar, demonstrates a 25–30% decrease in DON from its parent cultivar 'CDC Kendall'. 'Taylor', a doubled haploid hulless malting variety, was selected from a segregating cross (Legge et al. 2013) using an anther culture and growth media with multiple mycotoxins. This cultivar also displays reduced DON content within the hulless class, which is the least toxic type of barley, attributable to the physical separation of the hull, which retains half of all kernel mycotoxins (Clear et al. 1997). A microspore technique was also developed at AAFC Brandon and applied to the development of breeding populations through IVS (Banik et al. 2005). This success of IVS was genotype specific, with the resistant lines identified under sporadic occurrence rather than as results with a generalized effect (Legge et al. 2004). While loss of resistance with IVS cultivars can occur, the resistance of these cultivars, such as 'Norman' and 'Taylor', has shown stability over time.

With the routine development and application of molecular markers in plant breeding during the late 1990s, a large number of bi-parental mapping studies have been conducted in an attempt to identify QTL associated with FHB resistance and low DON accumulation (e.g. as reviewed by Massman et al. 2011; Foroud et al. 2019b). Multiple resistance sources have been investigated, including six-rowed 'Chevron' (de la Peña et al. 1999; Ma et al. 2000; Canci et al. 2004), two-rowed 'Aza-fran' (CMB 643) (Zhu et al. 1999), CI 4196 (Horsley et al. 2006), 'Frederickson' (Mesfin et al. 2003; Smith et al. 2004), 'Gobernadora' (Shenmai 1 or Zhenmai 1) (Zhu et al. 1999), 'Harbin' (Hori et al. 2006; Sato et al. 2008), 'Russia 6′ (Hori et al. 2005), 'Zhedar 2′ (Dahleen et al. 2003), and 'Zhenongda 7′ (Yu et al. 2010). These studies have identified significant QTL on all seven chromosomes of barley and some in multiple chromosomal regions. The QTL associated with FHB have often been coincidental with those for DON, but this is not universal, which demonstrates the difficulties in breeding for this disease where resistance for both characters is desirable. In general, these QTL have tended to show minor effects, subject to genotype and environment interactions (*i.e.* environmentally specific interactions) and display large confidence intervals (> 20 cM), limiting their applications for breeding.

While a number of QTL have been identified for FHB severity and/or DON content, many have coincidental occurrence with adverse agronomic characters and thus have not been useful in breeding programs (Huang et al. 2018). Chromosome 2 H has been a source of major QTL, occurring in bins 8 and 10 (defined as *Qrgz-2 H-8* and *Qrgz-2 H-10*, respectively). However, these QTL are associated with the heading date and/or plant height (de la Peña et al. 1999; Ma et al. 2000; Dahleen et al. 2003; Mesfin et al. 2003; Horsley et al. 2006; Lamb et al. 2009; Huang et al. 2018), and the *Vrs1* locus controls the two-row spike type. The short arm of chromosome 2 H possesses multiple major genes that control photoperiod response (*Ppd-H1*, Laurie et al. 1994) and early maturity (*Eam6*, Franckowiak and Konishi 2002). The lack of adequate genetic resolution in many experiments has made it difficult to define conclusively whether two-row morphology is due to genetic linkage or pleiotropy; however, fine-mapping analysis of *Qrgz-2 H-8* has implied that tight linkage is the possible mechanism (Nduulu et al. 2007). Furthermore, resistance derived from accession CI 4196 was incorporated into a six-row background in the germplasm line 6NDRFG-1 (PI 615 583), with a level of resistance comparable to its parental line (Urrea et al. 2002). The QTL associated with *Vrs1* was also identified in a six-row association mapping population, providing evidence of an independent genetic control (Massman et al. 2011). Hori et al. (2006) and Sato et al. (2008) also identified a locus on 2 H in the peri-centromeric region using two-row by two-row crosses. The QTL contributed by 'Harbin' were found in proximity to the cleistogamy locus (*cly1*/*Cly2*), which determines the open/closed flowering type, implicating its involvement in resistance. Yu et al. (2010) reported a locus on the 2 H chromosome in bin 14 (defined as *Qrgz-2 H-14*), which was derived from an adapted North American parent. This locus, which described 14% of the phenotypic variation, was not associated with the heading date or plant height.

Along with the major QTL observed on 2 H, genetic studies involving 'Chevron' have identified QTL on chromosomes 1H (de la Peña et al. 1999; Ma et al. 2000) and 7 H (Ma et al. 2000); however, these are also associated with late heading and tall stature. Horsley et al. (2006) identified a locus on chromosome 4 H (bin 2) derived from Chinese accession CI 4196 that explained 9–14% of the variation for DON accumulation and was subsequently designated as *QDON-4 H-2*.

A locus on chromosome 4 H was also detected in a study by Zhu et al. (1999), which was associated with plant height but not heading date. A locus derived from the Chinese accession 'Zhedar 2′ that was identified on chromosome 6 H (Dahleen et al. 2003) has been associated with late heading. Another locus associated with kernel discoloration on 6 H (Canci et al. 2004) is accompanied by elevated protein content (Canci et al. 2003), a character considered to be highly undesirable for malting barley. Huang et al. (2018) used a 93-entry RIL population with partial resistance derived from the elite cultivar 'Rasmusson' to investigate QTL for FHB resistance and DON accumulation in the context of associated agronomic traits. They found QTL and agronomic character associations similar to those contributed by 'Chevron'; however, a native and minor locus on 3 H (bin 4) donated by 'Rasmusson' was found to lower the DON content and was independent of plant height. The correlated response of negative characters (via pleiotropy or linkage disequilibrium) has highly limited MAS for low FHB and DON in barley. Of the many QTL reported for FHB resistance (78) and DON accumulation (42), only a couple demonstrate independence from other characters (Steffenson et al. 2016). Introgression in the breeding programs via screening methods using molecular markers that incorporate multiple agronomic traits might help with achieving durable resistance.

### *Modern biotechnologies and how they facilitate FHB research*

Technological improvements in genomics have made it possible to contend with the common difficulties for cereal crop species of the *Triticeae* tribe, which are considered challenging to work with given their extremely large size and numerous repetitive elements throughout their genome. Efforts by the International Barley Genome Sequencing Consortium in 2012 have resulted in the production of the first high-quality reference assembly for the 5.1 Gbp barley genome (Beier et al. 2017; Mascher et al. 2017). With the creation of this biotechnological tool, new possibilities exist for plant breeders to exploit this information and develop improved and adapted barley cultivars for use in sustainable production systems (Smith et al. 2018). Barley breeders now have convenient access to high throughput applications and the evaluation of breeding populations with development of genotyping array barley platforms, including diversity array technology (DArT; Wenzl et al. 2004), SNP assays such as Illumina GoldenGate (Close et al. 2009), and Illumina Infinium iSelect Custom Genotyping BeadChip assays of 9000 (Comadran et al. 2012) or 50 000 (Bayer et al. 2017) markers. However, the level of success depends greatly on the use of appropriate phenotyping methods. The advances in phenotyping methods, like remote sensing and machine learning (Mutka and Bart 2015; Willocquet et al. 2017; Odilbekov et al. 2018), could be harnessed to achieve durable disease resistance in wheat and barley breeding.

Resistance to FHB and DON production is complex and controlled by numerous genes, which makes evaluation difficult and costly and thus represents ideal targets for GWAS. Association mapping offers potential to identify resistance QTL that are less problematic in regard to unfavourable linkages, as seen in bi-parental studies involving exotic cultivars. Massman et al. (2011) utilized a GWAS panel consisting of 768 lines from advanced breeding populations from four USA barley breeding programs in the Upper Midwest to analyze associations of FHB and DON using the Illumina GoldenGate bead array SNP assay (BOPA1; Close et al. 2009). Several minor QTL explaining 1–3% of the phenotypic variation for FHB (4) or DON (8) were identified, but genomic regions were less coincident with heading date and/or plant height. The study identified strong clustering between breeding programs and row types, indicating little crossbreeding between groups. Very few QTL were detected in two-row vs. six-row sub-populations, probably due to less phenotypic variation overall within the two-row class and/or gene expression within different genetic backgrounds. Mamo and Steffenson (2015) evaluated a diverse set of 298 Ethiopian and Eritrean barley landraces with an Illumina iSelect Infinium 9000 SNP array (BOPA1 and BOPA2; Comadran et al. 2012). The phenotypes of these accessions were analyzed for multiple agronomic characters as well as in terms of FHB and the DON content by inoculation with a mixture of 19 isolates of *F. graminearum*. While the study identified QTL for reduced FHB and DON, as seen in a previous study, negative associations with agronomic characters were not present, indicating that this germplasm could be useful in breeding programs without the confounding effects related to the heading date or plant height. Bedawy et al. (2018) conducted leaf and spike disease assays with a diversity panel comprised 140 genotypes in combination with DArT and iSelect SNP marker assays, identifying QTL for each character on chromosomes 1 H and 5 H, respectively. They also identified positive epistatic interactions contributing to

disease reduction. While GWAS of FHB resistance in barley have generally identified many genes of minor effect, a more comprehensive approach to breeding such as genomic selection may be more productive (Massman et al. 2011).

Lande and Thompson (1990) introduced the concept of using genome-wide molecular markers to improve quantitative traits. Limitations in the molecular marker methodologies at the time could not support high throughput applications. Genomic selection, as conceived by Meuwissen et al. (2001), is a breeding approach founded on the principle that with dense enough marker coverage, each allele contributing to a character will be in linkage disequilibrium with a polymorphic molecular marker, e.g. a SNP marker. Comprehensive summation of marker effects across entire genomes may be used to predict the merit of characters for individuals and to perform candidate selection. Many complex models have been pursued to improve the accuracy of the method (Desta and Ortiz 2014; Wang et al. 2018a); however, simplistic models may often be adequate (de Los Campos et al. 2013). Basic principles involve synchronized phenotyping of a 'training' population that differentiates for a character of interest and genotyping via genome-wide molecular markers, e.g. SNP markers. Character-marker associations are used to calculate a genomic estimated breeding value (GEBV) for individuals in a population for which the breeder wishes to perform selection based on genomic information alone. As predictions are based on associations formed in the 'training set', the accuracy of the initial phenotyping, along with a close genetic relationship to that for which selection is applied, are important determinants of prediction accuracy (Habier et al. 2013). While this approach has been more readily adopted by animal breeders, it has recently gained favour in the plant-breeding community and is expected to revolutionize the breeding of crops with complex characters (Bhat et al. 2016; Crossa et al. 2017; Robertsen et al. 2019).

Due to the global nutritional and economic importance of wheat, significant efforts have been devoted to the genetic improvement of FHB resistance in wheat. Literature reviews (Buerstmayr et al. 2009, 2019) and a meta-analysis (Venske et al. 2019) have identified numerous QTL from studies conducted over the past two decades. While molecular markers are now commonly used in breeding for the incorporation of several major QTL (*i.e. Fhb1, Fhb2, Qfhs.ifa-5A*), it is recognized that the breeding value of QTL may have been over-estimated and that QTL may interact in complex ways in field situations. Genomic selection has been used as an alternative or complementary method to MAS for breeding FHB-resistant wheat cultivars (reviewed by Steiner et al. 2017; Buerstmayr et al. 2019). The genomic prediction of FHB and/or DON shows great potential, where several studies have demonstrated moderate prediction accuracies with hexaploid (Rutkoski et al. 2012; Arruda et al. 2015; Jiang et al. 2015; Mirdita et al. 2015; Hoffstetter et al. 2016; Dong et al. 2018) and durum wheat cultivars (Steiner et al. 2019; Moreno-Amores et al. 2020). Genomic selection models may show advantages over traditional MAS through the benefit of higher-prediction accuracy (Arruda et al. 2016a). Overall, the implementation of genome-assisted breeding strategies within wheat to improve FHB resistance is very promising in consideration of the polyploidy and immensity of the genomic size of approximately 17 Gb (Shi and Ling 2018).

Emerging genomic tools for barley offer prospects for sustaining barley improvement in the face of difficult breeding objectives such as FHB resistance (Smith et al. 2018). Prior to implementation, multiple studies have performed *in silico* analysis for the pre-evaluation of genomic prediction with six-row barley cultivars. Real data for 1325 SNP markers (BOPA1, Close et al. 2009), identified in 863 barley breeding lines, were used in a study with 100 hypothetical QTL for a character of interest, where moderate prediction accuracies endorsed genomic selection in barley breeding programs (Iwata and Jannink 2011). Simulation was further implemented through the application of phenotypic information for FHB and DON content in six-row barley lines, concluding that due to excessive linkage disequilibrium, marker numbers could be reduced to as little as 384 within a population of 200 with a minimal effect on genomic prediction (Lorenz et al. 2012). Increasing population size by the addition of neighbouring barley breeding programs, where little genetic information is exchanged, showed no advantage when incorporated into the training population (Lorenz et al. 2012; Lorenz and Smith 2015). The positive preliminary results of simulated studies have encouraged further research into the application of genomic prediction in breeding methods to reduce the incidence of FHB in cereals.

Sallam and Smith (2016) evaluated multiple genomic prediction models of FHB and DON for a dynamic six-row barley population comprised 647 breeder lines. They concluded that prediction accuracy was not improved in models that were more complex. Abed et al. (2018) also demonstrated successful genomic selection for six-row barley, where models including both additive and epistatic components demonstrated better predictability. These

studies documented moderate genomic predictions for FHB and DON in barley, supporting genomic selection applications. Both studies also demonstrated significant reductions in the set of genome-wide markers, which could be implemented without a significant loss of predication accuracy. Genomic selection for increasing FHB resistance and lowering DON content in six-row barley could make use of more conservative genomic panels with reduced targets. In two-row barley, current efforts are under way using both Illumina Infinium iSelect Custom Genotyping BeadChip assays of 50 000 and GBS (Tucker et al. 2017, unpublished data).

A more ambitious goal is the application of genome-wide markers for informative parental selection. Modern methods (Mohammadi et al. 2015) which utilize phenotype and genotype relationships and informative segregating markers exhibit improved prediction of genetic variance ($\sigma^2_G$). As such a method, 'PopVar' has demonstrated reasonably accurate prediction of $\sigma^2_G$ for FHB severity within 40 historic, six-row, bi-parental-breeding populations (Tiede et al. 2015). Abed and Belzile (2019) used 'PopVar' to predict yield and DON *in silico* for the simulated progeny of 245 pairwise crosses of six-row barley parents in a training population, and then validated these crosses using data from registration trials in eastern Canada. Neyhart and Smith (2019) used a training population of two-row barley lines to predict superior parental combinations, which were validated through phenotyping 27 bi-parental populations. These studies have been able to predict progeny means well, but with genetic variance to a lesser degree (Abed & Belzile 2019). Recently, preliminary results using deep learning methodologies with two-row barley for the genomic prediction of FHB and DON content have shown some improvements over classical methods (Tucker et al. 2020). Overall, such studies support the feasibility of using genome-wide markers to determine better choices for crossbreeding.

### *Use of modern genomic tools to combat FHB and DON accumulation*

While cereals exhibit defence responses to *F. graminearum* invasion, *i.e.* the expression of pathogenicity-related proteins, these responses generally either do not occur quickly enough, with enough abundance, or in the required tissues. Wheat and barley have been transformed with a number of targets, thereby conferring anti-fungal protein products (reviewed by Dahleen et al. 2001). Most targets have been fungal-specific cell wall components, such as chitinase (*PR-3*) and β-1,3-glucanases (*PR-2*), thaumatin-like proteins (*PR-5*), thionin (*PR-13*), and ribosome-inactivating proteins (RIPs), which target/inhibit protein synthesis in fungal cells. Abebe et al. (2006) demonstrated application of the *Lem2* gene promoter in barley for the tissue-specific expression of transgenics, which could restrict transgene expression within organs important to *Fusarium* defence (lemma/palea and coleoptiles), thereby conserving energy in the defence response. The introgression of antimicrobial peptides driven by several tissue-specific promoters into the susceptible wheat cultivar 'Fielder' allowed the development of an elite wheat line expressing two antimicrobial peptides (MsrA2 and 10 R) that increased resistance to FHB and powdery mildew (Badea et al. 2013). These peptides included *Lem1, GstA1WIR1a*, or *Ltp6*, targeting the lemma/palea, leaves and spikes, and epicarp and endomembrane systems. The main advantage offered by antimicrobial peptides is that they provide their host with a rapid non-specific defence against invading microorganisms, conferring a broad-spectrum (antibacterial, antiviral, antifungal) and powerful resistance to infection. The genetic engineering of cereal crops has also focused on the de-toxification of DON. Trichothecene genes (TRI genes) have been characterized well in terms of their function. *Fusarium graminearum* uses the *TRI101* gene to protect itself from DON through acetylation of the C-3 hydroxyl group. It was suggested that host plants expressing this gene would also lead to reduced toxicity (Kimura et al. 1998). While *TRI101* trans-genes were able to reduce FHB and DON in wheat (Okubara et al. 2002) and barley (Manoharan et al. 2006), this mechanism did not confer resistance in the field, possibly due to reconversion to DON *in planta*. Transgenic wheat plants with the barley UGT gene *HvUGT13248* display higher levels of resistance to FHB (Li et al. 2015) and crown root rot (Mandalà et al. 2019). As ribosomal protein L3 (RPL3) is so essential to biological function, it is generally conserved; however, it is also the target of DON binding, which interferes with protein synthesis. Investigations have been conducted with altered RPL3 from rice (Harris and Gleddie 2001) or tomatoes (Mitterbauer et al. 2004) with variable success. The epoxide on C12/C13 is the primary toxicity determinant of DON (Eriksen et al. 2004). Several bacterial species produce enzymes that have the ability to de-epoxidize DON to a non-toxic form and are used as amendments in industrial processing to detoxify grains. Genes coding for enzymes that confer de-epoxidation of DON would represent excellent targets for the transformation of cereals.

Technological advancements in gene editing platforms such as clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 offer new potential ways to remove susceptibility targets from host genomes.

CRISPR-mediated genome editing was applied to a wheat ortholog (*TaNFXL1*) of the *A. thaliana* trichothecene-responsive defence gene *NFXL1*. *TaNFXL1* is a transcription factor that represses *F. graminearum* resistance and thus represents a potential breeding target to reduce FHB. CRISPR editing of additional susceptibility (*TaABCC6*) and resistance (*TansLTP9.4*) targets has been demonstrated (Cui et al. 2019). Su et al. (2019) showed that deletion of the susceptibility gene *TaHRC* (putative histidine-rich calcium-binding protein) via CRISPR-Cas9 increased resistance. Lipoxygenases are associated with jasmonic acid-mediated defence, which attenuates the salicylic acid response, thus representing targets for gene editing (Borisjuk et al. 2019). Wang et al. (2018b) demonstrated that CRISPR editing is possible for the *TaLpx-1* gene (9-lipoxygenase). The CRISPR-Cas9 system has been successfully applied to edit barley (Lawrenson et al. 2015; Gasparis et al. 2018). FHB-resistance related susceptibility targets such as putative 2-oxoglutarate Fe (II)-dependent oxygenase (*2OGO*) and ethylene insensitive 2 (*EIN2*) are presently being evaluated (Low et al. 2019, 2020).

As mentioned above, RNAi is a relatively new genomic tool for silencing genes that may promote disease in plants, and provides new potential in the battle to control FHB in cereals (Machado et al. 2018). RNA molecules are used to inhibit gene expression or translation by targeting mRNA through the introduction of sequence-specific double-stranded RNAs (dsRNA). Koch et al. (2013) demonstrated reduced growth in *F. graminearum* through the HIGS of cytochrome P450 lanosterol C14 alpha-demethylase-encoding (*CYP51*) genes, which are essential for ergosterol biosynthesis. Targeting chitin synthase via HIGS demonstrated reduced infection in wheat (Cheng et al. 2015), while a small *F. graminearum* RNA (Fg-sRNA1) silenced the wheat resistance Chitin elicitor gene (*TaCEBiP*) in *Nicotiana benthamiana* to enhance *F. graminearum* infection (Jian and Liang 2019). Chen et al. (2016) investigated the HIGS of the β-1,3-glucan synthase gene *FcGls1* of *F. culmorum*, which induced cell wall abnormalities expressed as swollen hyphae. Baldwin et al. (2018) demonstrated that RNAi vectors could also target a positive regulatory gene (*TRI6*) in the trichothecene cluster of *F. graminearum*, which reduced the expression of *TRI5, i.e.* the first gene in the DON production pathway. RNAi can also be applied in a non-transgenic approach through external application via spray-induced gene silencing (SIGS). Exogenous formulations of long dsRNA or siRNAs (short interfering RNA) can be applied and subsequently taken up by cells (host or pathogen target). Koch et al. (2016) demonstrated in Arabidopsis and barley that spraying long dsRNAs targeting *CYP51* genes facilitated disease control. This method is publicly appealing due to its non-transgenic nature, high specificity, potential for application against multiple pathogens, and the ephemeral nature of applied RNA molecules in the environment.

## Field-based tools in FHB management

The management of FHB is facilitated by tools that can be applied in the field. Field data, as opposed to data obtained from greenhouse studies, are understandably more reliable in terms of drawing solid conclusions that can be integrated in management strategies. Field-based tools in FHB research include forecasting tools, diagnostic methods, phenotyping/genotyping assays, pathogen community and mycotoxin profiling, airborne inoculum potential analysis, and imaging. The development of these tools is progressing at a very fast pace in FHB research and choosing the right tool would depend on a number of factors, including the affordability and sustainability in a particular environment.

### *Prediction tools*

Forecasting tools are integrated mostly as web-based tools for FHB disease prediction. In the United States, the Fusarium Head Blight Prediction Centre (http://www.wheatscab.psu.edu/) is a multi-institutional collaborative web-based platform funded by the USDA/ARS and the United States Wheat and Barley Scab Initiative that allows for risk assessment based on certain parameters like the geographic location, crop type, and weather. A web-based FHB predictive tool (bdbnet.bdb.be/pls/apex/f?p = 133:1:0) using various models was also developed in Belgium using agronomic variables and weather data collected over a period of nine years (2002–2011) (Landschoot et al. 2013). Prediction models enable farmers and other stakeholders to make informed decisions for fungicide application and marketing. The availability of such models should serve as motivation for other regions to develop similar models based on the geographic parameters that favour FHB development in their given locality. A similar internet-based software package (FusaProg) for FHB forecasting was developed for winter wheat in Switzerland (Musa et al. 2007). FusaProg is a decision support system that forecasts DON content based on cropping factors, previous crops, soil/debris management, cultivar resistance, weather conditions and the crop growth stage. In addition, FusaProg is able to forecast the DON contents of particular fields. Currently, efforts are under way in

Canada for the development of risk models for the Prairies to determine the risk of FHB infection in spring and winter wheat. These models will contribute to improved crop management and profitability in the cereal industry by identifying crop varieties and stages that are at risk of FHB, whereby timely fungicide applications for suppression can be utilized to mitigate the risk and consequent yield and quality impacts. For example, the current model used in Manitoba provides a general assessment of FHB risk across broad areas based on the weather conditions during the previous seven days. The new models will improve FHB risk assessment for a specific location by incorporating site-specific data (Bullock & Fernando, unpublished data).

### *Diagnostic tools and microbial community profiling*

Although most diagnostic tools in FHB research involve molecular methods that are carried out in the laboratory, the materials used for these methods require systematic methods for sampling and collection. This goes a long way in determining the accuracy and reliability of the laboratory results. A rapid wheat scab diagnostic system based on an Android mobile phone was developed recently in China (Zhang et al. 2019). This model was based on analysis of the colour, texture, and shape of the *Fusarium*-damaged kernels (FDKs). Real-time image capturing allows rapid and non-destructive prediction of FHB severity in the field. *Fusarium* communities, including pathogenic species, can be elucidated by metabarcoding, which also shows specific trends, noticed in terms of temporal and special shifts (Cobo-Díaz et al. 2019a). Metabarcoding can also be combined with co-occurrence network analysis, which can provide information regarding potential antagonists that can be tested for biocontrol activities. A metabarcoding/co-occurrence network analysis approach that combined *Fusarium* and bacteria primers was developed to study microbial communities in FHB-infected maize stalks, with the aim of finding potential bacterial biocontrol agents (Cobo-Díaz et al. 2019b).

### *Airborne inoculum potential*

The epidemiology of FHB in small grain cereals is facilitated by the production of various inoculum propagules, such as mycelium, chlamydospores within crop residues, and airborne ascospores, which are mostly dispersed by the wind and consequently cause infection (Gilbert and Fernando 2004; Osborne and Stein 2007). Isolation of *Fusarium* pathogens in the field is not easy, as the cultures formed are always replete with other airborne saprophytes. A selective medium based on tolerance to toxoflavin has been developed to isolate *F. graminearum* in the field by exposing the medium to the air around wheat fields (Jung et al. 2013). The importance of an airborne inoculum in FHB epidemics has also been highlighted by the work of Hellin et al. (2018). They quantified airborne inoculum trapped at different wheat growth stages and found that high inoculum quantities correlated strongly with *F. graminearum* infection and DON production at anthesis. Further proof is required in terms of fungicide spraying before or during anthesis to manage FHB in wheat.

### *Field-based agronomic practices*

Agronomic practices can also be tools that can have important effects in terms of FHB management. Tillage conservation and the preceding crop both play very important roles in terms of the proliferation of *Fusarium* pathogens in crop debris. Koch et al. (2006) analyzed several agronomic factors, both alone and in combination, to decipher the factors with the greatest influence with respect to DON reduction in winter wheat crops. The results showed that the use of resistant cultivars, together with conservation practices and as well as fungicide application at anthesis, produced the best outcomes with respect to reduced DON in winter wheat. These findings were recently reinforced by an extensive study conducted in FHB-susceptible and resistant spring and winter wheat cultivars at seven different sites across the Canadian Prairies over three years under both natural and artificial infection scenarios (Ye et al. 2017). The study also highlighted the advantages provided by winter vs. spring growth habits with respect to FHB and grain yield.

### *Fungicidal control of FHB*

The demethylation inhibitor (DMI) group of fungicides (tebuconazole, prothioconazole, and metconazole) has been shown to be efficient in the control of FHB in wheat and barley (Paul et al. 2008; D'Angelo et al. 2014). Fungicide application for FHB management is most effective when applied at anthesis, and applications made six days after anthesis have been reported to be the most effective with respect to disease incidence and DON reduction (D'Angelo et al. 2014). Multi-year studies of fungicide efficacy when used in combination with different levels of resistance reveal that host resistance plays a major role in the interaction between the host,

pathogen, and fungicide (Amarasing Amarasing He et al. 2013; Paul et al. 2019). Studies of this nature further support the need for an integrated approach for FHB management.

### *Imaging and visual assessment tools*

Visual observation is often the method used to determine phenotypic traits and estimate FHB severity in wheat grains; however, this is not the case for barley, where FHB and DON show low correlations and FDKs and DON show even lower correlations (as reviewed by Foroud et al. 2019b). More recently, a method using digital image analysis of whitened kernel surfaces (WKSs) to assess FDKs and DON content was proposed for wheat (Ollier et al. 2019). The WKSs from a vast number of wheat and triticale lines tested correlated well with the DON content. This timely, fast, and efficient tool would facilitate line selection in breeding programs. The phenotyping of wheat lines in FHB resistance-breeding trials is often a cumbersome, costly, and time-consuming process. Finding new techniques that can overcome these challenges is an area of interest for both plant pathologists and breeders. A deep neutral network and colour imaging phenotyping system that assesses FHB in the field based on colour image processing techniques with diseased wheat spikes has been developed recently (Qiu et al. 2019b). Techniques like this have the ability to hasten the long process for FHB resistance breeding, where thousands of lines are usually tested in field trials. One such imaging technique is hyperspectral imaging. Hyperspectral imaging techniques have huge potential in terms of separating healthy wheat grains from grains with FHB (Zhang & Ji 2019). Hyperspectral imaging is a non-destructive method for discriminating wheat grains. Mycotoxin contamination in wheat grains is normally carried out when using expensive high-performance liquid chromatography (HPLC) methods, which are also time consuming. Visual assessment coupled with computer-assisted image analysis of wheat spikes was developed to predict mycotoxin contamination for wheat in France (Leplat et al. 2018). Mycotoxin prediction based on this approach was well correlated with the results from HPLC-based mycotoxin contamination assays. Although this tool needs to be tested in multiple environments, it shows potential promise as a cost-effective alternative to HPLC mycotoxin assays.

## Conclusions and future perspectives

The pathogens causing FHB can be devastating to wheat and barley, as they have the ability to evolve rapidly in spite of different management strategies. Spread of FHB is enhanced by the ability of *Fusarium* ascospores to disseminate via air over long geographic areas. The development of resistant varieties of wheat and barley could play a major role in combating FHB epidemics in the future. Germplasm exchange between breeding programs in different regions of the world would ensure the development of cultivars with both exotic and local sources of resistance that are more effective against the disease. This approach has been successful in terms of developing 'Sumai 3′-derived (originally developed in China) wheat cultivars with moderate resistance against FHB in different parts of the world. Breeders can speed up breeding programs by harnessing the availability of next-generation sequencing technologies. Furthermore, MAS can help with gene pyramiding, which promotes durable, long-term resistance. We advocate an integrated approach for the management of FHB, which includes the use of resistant varieties, good agronomic practices, efficient disease forecasting models, and research to mitigate the effects of FHB in both wheat and barley production globally. In summary, this review has provided information that will assist wheat and barley researchers, students, plant pathologists, and breeders in terms of the current resources available for the study of FHB in wheat and barley.

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