# Monoclonal Antibody 5B2

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Candidiasis (either mucocutaneous or systemic) is an opportunistic infection caused mainly by *Candida albicans*, a yeast and natural commensal of the human digestive tract and vagina. Unlike true pathogens, the presence of yeasts alone does not indicate their pathogenic character, which depends essentially on the susceptibility of the host and the expression of pathogenicity factors by some yeast strains. It is therefore essential to have markers associated with pathogenicity to understand the mechanisms of infection and to diagnose these infections as accurately as possible. The development of hybridoma technology/advent of monoclonal antibodies (mAbs) led to considerable progress in answering some of these questions. Among the monoclonal antibodies (mAbs) developed, mAb 5B2 allowed us to make considerable progress in understanding the mechanisms of pathogenesis and also contributed to the diagnosis of candidiasis and the tracing of more pathogenic strains.

monoclonal antibody | diagnosis | mAb 5B2 | yeast | *Candida albicans*

## 1. Immunochemical Identification of mAb 5B2 Epitopes, Their Carrier Molecules and Genes Involved in Their Synthesis

Unlike many mAbs generated from the immunisation of mice with killed yeasts or molecules extracted from yeasts, mAb 5B2 was generated from an experimental infection in a rat [1].

As the epitope was found to be present in mannan, a major *C. albicans* cell wall polysaccharide both quantitatively and qualitatively, its precise nature was determined through a series of immunobiochemical studies concerning this molecule. These studies consisted of sequential depolymerisation and nuclear magnetic resonance analysis and were based around the impressive pioneering structural studies conducted in Japan by Prof. Suzuki's group on *Candida* mannans or, more exactly, phosphopeptidomannans (PPMs), focusing on the so-called antigenic factors allowing Candida species or serotype identification by direct agglutination [2][3][4]. The 5B2 epitope was identified among the β-1,2-linked mannoside series [5][6][7][8][9]. These structures are rare in the living world and are expressed in large quantities in the most pathogenic species of the genus *Candida*, namely *C. glabrata* and *C. tropicalis*, which are isolated second and third, respectively, after *C. albicans* from human disease. A considerable amount of information on β-1,2 oligomannosides has been gathered by S. Suzuki's group according to their relation with antigenic factors [10] and expression in different strains depending on growth conditions showing important changes related to pH [11] and temperature [12], triggering the yeast to hyphal transition [13]. An impressive synthesis gathering all this information was presented in a review published in 2012 [4]. The precise identification of

the 5B2 epitope showed reactivity against a minimal degree of polymerisation of two β-1,2 linked mannoside residues, thus corresponding to antigenic factor 5 and in part antigenic factor 6 [14].

Western blot profiles revealed that the 5B2 epitope was expressed on a large number of *C. albicans* molecules [15] distributed among very high relative molecular weight polydispersed material containing large amounts of polysaccharides and bands with lower molecular weight and better resolution in gels, corresponding to mannosylated proteins. These patterns were observed for several other pathogenic *Candida* species, with each having specific mapping of the 5B2 epitope [16]. In turn, an analysis of these profiles led to the discovery of concanavalin A-unreactive glycoconjugates with no protein moiety and to the identification of a glycolipid we named phospholipomannan (PLM) [17]. PLM was then studied extensively and characterised as a cell wall molecule belonging to the manno-inositol-phosphoceramide family [9][18][19][20][21].

Refinement of the methods of extraction of *C. albicans* cell wall mannoproteins based on the knowledge of their mode of insertion (PPM, glycosylphosphatidylinositol (GPI)-anchored proteins with internal repeats (PIR proteins and secreted proteins)) led to a complete mapping of the molecules containing the 5B2 epitope, among which were well known “proteins” described as virulence factors, including Hwp1 and HSP 70 [22]. mAb 5B2 mapping of β-mannose epitopes in the mannoproteins of different cell wall fractions of mutants defective in the map kinase pathway revealed its importance in regulating the exposure of different surface anomery and modulation of the immune response [23].

Finally, mAb 5B2 contributed uniquely to the discovery and identification of the nine members of the gene family encoding β-mannosyl transferases (BMTs 1–9), responsible for the sequential addition of β-Mans on different carrier molecules. This has significantly improved our understanding of the β-Man biosynthetic pathway in *C. albicans* [24]. Further definition of BMT functions was achieved through sequential deletion in the strain BWP17 by PCR gene targeting. Briefly, β-Man transfer is under the control of BMTs 1 and 3 for the acid-stable fraction of PPM and BMTs 2, 3 and 4 for the acid-labile fraction. None of these four enzymes act on PLM, nevertheless BMTs 5 and 6 are specifically involved in the β-mannosylation of PLM. Concerning the O-mannosylation of cell wall mannoproteins, this depends on BMTs 1 and 3 [25][26][27][28]. Gene deletion of BMTs 7–9 was inconclusive and has not been the subject of specific studies to date. Only transcriptome analysis carried out to decipher *C. albicans* iron homeostasis mentions BMT 7 and BMT 9 in alternative genetic programs adapting to blood stream versus gut environments [29][30].

Recent developments in this area of research concern a highly pathogenic *Candida* species that emerged simultaneously in different countries worldwide with the characteristics of antifungal resistance and high virulence, leading to high rates of mortality among patients in intensive care units. This species, *C. auris*, was also shown to synthesise β-Mans [31].

Analysis of the distribution of the mAb 5B2 epitope confirmed high expression in some strains, placing *C. auris* in the same group as *C. albicans*, *C. tropicalis* and *C. glabrata*, namely the most pathogenic *Candida* species (Leroy et al., unpublished data to date). Experimentally, it has been shown that an IgG3 mAb specific for a β-1,2 linked

mannotriose described as protective against *C. albicans* [32] also protected mice against *C. auris* infection [33]. Addressing the general topic of the interplay between *Candida* and human antibodies, an impressive study demonstrated that *C. albicans* was able to shape the antibody repertoire though CARD9-dependent induction of host-protective antifungal IgG, including against *C. auris* [34]. On the fungal side, a mechanism of yeast surface modulation of antigens, including β-mannosides, able to direct macrophage responses was discovered to be under the control of *C. albicans* mitochondrial proteins [35]. In our view, these fascinating findings from this area of research deserve to be highlighted.

## 2. Cytological and Histopathological Analysis of mAb 5B2 Epitope Expression

In parallel to the identification of these molecules, mAb 5B2 was involved in studies aimed at localising the expression of 5B2 epitopes. At the population level, direct immunoperoxidase staining of *C. albicans* colonies grown on agar revealed an unforeseen complex expression of the epitope distributed according to different sectors [36]. Immunofluorescence and confocal microscopy studies revealed a complex expression due to the multiplicity of molecules differently expressing the epitope on yeasts and hyphal forms at a given time in the cell cycle [37]. Among these, shedding of PLM from the cell wall on contact with host cells was demonstrated unambiguously [38] [39]. mAb 5B2 was used early on in histopathological studies to assess the presence of invasive foci of *Candida* in different clinical situations and experimental models [40]. At the gut level, it was used to assess colonisation by yeast species expressing β-mannosides and to identify host and yeast backgrounds modulating intestinal interactions [41][42].

At the ultrastructural level, transmission electron microscopy studies on *C. albicans* ultrathin liquid nitrogen frozen sections probed with 5B2 directly coupled to gold particles showed its localisation within cytoplasmic vesicles merging with the cell membrane and crossing the cell wall through channels [43][44]. The merging of these channels at the cell wall surface corresponded to the “patchy” distribution of β-Man epitopes reported by other authors in immunofluorescence studies [45].

## 3. Contribution of mAb 5B2 to the Analysis of the Immunological Interface between C. albicans and 5B2 Epitopes or Molecules Expressing These Epitopes—Identification of the Ligands and Triggering Consequences

As a counterpart to the identification of the 5B2 epitope and the *C. albicans* molecules expressing these specific motifs, mAb 5B2 was involved in experiments to assess the properties of these molecules. In these immunobiological studies, mAb 5B2 was the probe used as a reference. One of the major findings was the identification of Galectin-3 (Gal-3) as the mammalian receptor for β-mannosides [37][38][39][46][47][48][49][50][51][52][53][54] [55]. Although research on Gal-3, known as Mac2 antigen, was limited at this time [52], Gal-3 is now established as a lectin playing an important role in numerous human diseases; its important pleiotropic roles have generated more

than 5000 papers. Interestingly, regarding *Candida* pathogenesis, circulating levels of Gal-3 appear to be markers of both infection and inflammation [56], a duality compatible with its ability to predict the recurrence of Crohn's disease after surgery associated with persistent inflammation and *C. albicans* colonisation [57]. Regarding relative importance of Gal-3 among other *C. albicans* receptors, its discovery at the end of the 1990s was among the first of a long list of what has been called later Pathogens Recognition Receptors (PRRs) as a counterpart of fungal Pathogen Associated Microbial Patterns (PAMPs). Only mannose receptor was identified at this time [58][59], as early as in the 1980s, so that differentiating at this time a and β mannose binding was important. To our knowledge, apart from MBL, which was described simultaneously in 2000 [60], other major receptors were identified later: Dectin-1 in 2001 [61][62][63]; first TLRs in 2002 [64][65]; DC-Sign in 2003 [66]; Dectin-2 in 2006 [67][68]. Comprehensive reviews regularly synthesized the importance of these interactions in shaping the host immune response [69][70][71]. Regarding the modulation liable to be linked to Gal-3, a reason to delve into this notion is that the presence of β-1,2-mannosides in N-linked mannan reduces the production of inflammatory cytokines by dendritic cells [72]. This seems of pathophysiological relevance since the morphological transformation of Candida conidia into hyphae form is characterized by a decrease in the amount of phosphodiesterified acid-labile β-1,2-linked manno-oligosaccharides, whereas the amount of acid-stable β-1,2 linkage-containing side chains does not change [13]. The corollary to these findings may be that Candida variants reacting with mAb 5B2 are unable to induce a robust proinflammatory and an appropriate mechanism of antigen presentation. This should be noticed because dendritic cells show a unique pattern of C-lectin type receptors to carry out non-opsonic phagocytosis and produce cytokines that tailor the microenvironment in the immune synapsis to initiate the adaptive immune response. This disappearance of β-Man is of importance regarding unmaking of α-Mans. This topic relates to the so-called ASCA, human antibodies revealed by *S. cerevisiae* mannan allowing the diagnosis of Crohn's disease but generated by *C. albicans* pathogenic phase [73]. These antibodies are indeed anti-oligomannose antibodies reacting with α-1,3 mannose at the non-reducing end of 2 or 3 α-1,2 linked mannose. Besides Crohn's disease, ASCA are associated with a strong inflammatory response in a wide range of human diseases, most of which are associated with fungal dysbiosis and a *C. albicans* overgrowth [74].

## 4. Construction of mAb 5B2 Epitope Synthetic Analogues (β-1,2 Oligomannoside Series) and Analysis of Their Biological and Immunological Properties

With regard to the difficulties in producing β-1,2 oligomannosides by sequential degradation of *C. albicans* PPM, synthetic analogues were produced by chemical synthesis. mAb 5B2 was used to assess their conformity with natural products through the development of chemical synthesis steps. These synthetic probes mimicking adhesins were shown to prevent *C. albicans* colonisation in experimental mouse models [53]. When coupled to biotin sulfone, it was possible to detect specific antibodies either on microspheres by multi-analyte profiling technology (Luminex) or surface plasmonic analysis [75]. A recent paper involving mAb 5B2 used the same technology to determine the structural basis for protective epitope specificity and to discriminate the humoral responses of infected versus colonised patients [76].

In a similar approach aimed at identifying the structures mimicking β-Mans, a phage library expressing random peptides was screened with mAb 5B2. The application of this phage display methodology led to the isolation of peptides presenting with the same specificity as β-Mans in terms of adhesion and immunogenicity [77].

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