

Immune responses to human fungal pathogens and therapeutic prospects

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Supplementary Table 1 | **Clinical features of the most prevalent human fungal infections**

Infection (most common fungal genera or species)	Fungal morphotype	Clinical presentation	Commonly affected patient population ^a	Annual global incidence	All-cause mortality	Geographic distribution	Current principles of treatment
Mucosal candidiasis ^b (<i>Candida albicans</i> , <i>C. dubliniensis</i> , <i>C. glabrata</i>)	Yeast (with pseudohyphae and hyphae depending on the species)	Oropharyngeal and/or oesophageal candidiasis	HIV/AIDS, corticosteroids	~3.3 million (HIV/AIDS only)	N/A	Worldwide	Topical or oral azoles; echinocandins (for azole-resistant <i>Candida</i> strains)
		Vaginal candidiasis	Healthy women, antibiotic use	~138 million			
Invasive candidiasis (<i>C. albicans</i> , <i>C. glabrata</i> , <i>C. tropicalis</i> , <i>C. parapsilosis</i> , <i>C. auris</i>)	Yeast (with pseudohyphae and hyphae depending on the species)	Candidemia	Critical illness (ICU), post-COVID-19	~750,000	~30-40%	Worldwide	Echinocandins; removal of central venous catheter
		Intra-abdominal candidiasis	Abdominal surgery				
		Disseminated candidiasis (liver, spleen, CNS, kidneys, eye, heart)	Neutropenia, corticosteroids, SOT (primary abdominal organs), low-birth weight premature neonates				
Invasive aspergillosis (<i>Aspergillus fumigatus</i> , <i>A. flavus</i> , <i>A. terreus</i> , <i>A. niger</i>)	Filamentous mold	Pulmonary or disseminated aspergillosis	Neutropenia, corticosteroids, HSCT, SOT (primarily lung), post-influenza or COVID-19, ibrutinib	~300,000	~30-50%	Worldwide	Voriconazole (first-line), isavuconazole or posaconazole; reduction of immunosuppression
		Allergic bronchopulmonary aspergillosis	Atopic individuals	~5 million ^c	N/A	Worldwide	Itraconazole and corticosteroids
Mucormycosis (<i>Rhizopus</i> , <i>Mucor</i> , <i>Rhizomucor</i>)	Filamentous mold	Sinopulmonary mucormycosis	Neutropenia, HSCT, corticosteroids, post-COVID-19	>10,000	~40-80%	Worldwide	Amphotericin B, posaconazole as step-down therapy; surgical debridement; reduction of immunosuppression
		Rhinocerebral mucormycosis	Diabetic ketoacidosis, post-COVID-19				

		Disseminated mucormycosis	Iron overload (e.g., deferoxamine iron chelation therapy)				
		Necrotizing skin infection	Direct inoculation (tornado victims)				
Chromoblastomycosis ^d (<i>Fonsecaea pedrosoi</i>)	Pigmented yeast	Skin and subcutaneous infections	Healthy individuals	~10,000 ^c	N/A	Worldwide (primarily in tropical and subtropical areas)	Itraconazole; surgical debridement
Phaeohyphomycosis (<i>Cladophialophora bantiana</i> , <i>Rhinocladiella mackenziei</i> , <i>Exophiala dermatitidis</i> , <i>Curvularia cunata</i> , <i>Bipolaris spicifera</i> , <i>Exserohilum rostratum</i>)	Melanin-bearing yeast-like forms and hyphae	Skin and subcutaneous infections	Healthy individuals	Emerging but unknown	Up to 70%	Worldwide	Amphotericin B or azole therapy
		CNS or disseminated infection	CARD9 deficiency, dectin 1 deficiency after trauma, HSCT, SOT, corticosteroids				
Cryptococcosis ^b (<i>Cryptococcus neoformans</i> , <i>C. gattii</i>)	Yeast	Pneumonia	AIDS, corticosteroids	~223,000 (HIV/AIDS only)	~20-70%	Worldwide	Amphotericin B (+5-flucytosine for CNS disease) followed by fluconazole; reduction of immunosuppression
		CNS or disseminated cryptococcosis	HIV/AIDS, HSCT, ibrutinib therapy				
Histoplasmosis ^b (<i>Histoplasma capsulatum</i>)	Dimorphic fungus (mold in soil, narrow-based yeast in infected tissue)	Self-limited pneumonia	Healthy individuals	~100,000 ^c	~10-50%	Midwestern United States, Central America, the Caribbean	Amphotericin B followed by itraconazole; reduction of immunosuppression
		Disseminated histoplasmosis (liver, bone, bone marrow)	HIV/AIDS, SOT, corticosteroids				
Blastomycosis (<i>Blastomyces dermatitidis</i>)	Dimorphic fungus (mold in soil, broad-based yeast in infected tissue)	Pneumonia	Healthy individuals	~3,000 ^c	<1-60%	Midwestern and Atlantic United States	Amphotericin B or itraconazole; reduction of immunosuppression
		Disseminated blastomycosis (skin, bone, mucosal surfaces,	HIV/AIDS, corticosteroids				

		genitourinary tract)					
Coccidioidomycosis ^b (<i>Coccidioides immitis</i> , <i>C. posadasii</i>)	Dimorphic fungus (mold in soil, spherules in infected tissue)	Self-limited pneumonia	Healthy individuals	~25,000 ^c	<1-60%	Southwest United States, Mexico	Fluconazole or amphotericin B; reduction of immunosuppression
		Disseminated infection (CNS, bone)	HIV/AIDS, corticosteroids				
Paracoccidioidomycosis (<i>Paracoccidioides brasiliensis</i>)	Dimorphic fungus (mold in soil, multipolar-budding yeast in infected tissue)	Pneumonia	Healthy individuals	~15,000 ^c	<5%	Latin America	Itraconazole, amphotericin B, or trimethoprim-sulfamethoxazole
		Disseminated infection (mucosae, skin, bone)	HIV/AIDS, corticosteroids				
Talaromycosis (<i>Talaromyces marneffei</i>)	Dimorphic fungus (mold in soil, yeast dividing by binary fission in infected tissue)	Pneumonia	Healthy individuals	~20,000	~20-30%	Southeast Asia	Amphotericin B followed by itraconazole; reduction of immunosuppression
		Disseminated infection (mucosae, skin, bone)	HIV/AIDS, corticosteroids				
Emergomycosis (<i>Emergomycetes pasteurianus</i> , <i>E. africanus</i>)	Dimorphic fungus (mold in soil, yeast in infected tissue)	Disseminated infection (skin, lungs, liver, spleen, bone marrow)	HIV/AIDS	Emerging but unknown	Up to 50%	Africa	Amphotericin B followed by itraconazole
Pneumocystosis ^b (<i>Pneumocystis jirovecii</i>)	Cysts and trophozoites	Pneumonia	HIV/AIDS, corticosteroids	~500,000	~20-80%	Worldwide	Trimethoprim-sulfamethoxazole; reduction of immunosuppression
		Disseminated infection (CNS, eye, gastrointestinal tract, skin)	HIV/AIDS				

^aAt-risk conditions caused by inborn errors of immunity or administration of immune pathway-targeted biologics are presented in-depth separately in Supplementary Tables 2 and 3; ^bAIDS-defining illness; ^cGlobal burden of infection; ^dWHO neglected tropical disease; ^eAnnual incidence of life-threatening infections; COVID-19, coronavirus disease 2019; CNS, central nervous system; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; N/A, not applicable; SOT, solid organ transplantation.

Supplementary Table 2 | **Key human inborn errors of immunity that predispose to fungal infection**

Gene [protein name if different] (chromosome)	Predominant cellular expression	OMIM no. (clinical syndrome if applicable) ^a	Mode of inheritance	Fungal infection susceptibility (mean frequency, when known)	Other clinical phenotypes	Diagnostic testing	Antifungal immunological defects (when known)
<i>Inborn errors of immunity that manifest with both mucocutaneous and invasive fungal infections</i>							
<i>CARD9</i> (9q)	Myeloid phagocytes and to a lesser extent epithelial cells	212050	AR (LOF)	CMC (~35%), CNS candidiasis (~30%), phaeohyphomycosis (~15%), extrapulmonary aspergillosis (~5%), skin mucormycosis (rare), onychomycosis (~50%), deep dermatophytosis (~40%)	None	Genetic sequencing	Decreased peripheral blood T _H 17 cells, impaired pro-inflammatory cytokine responses by PBMC and microglia, impaired neutrophil recruitment to the CNS, impaired neutrophil killing of unopsonized <i>Candida</i> yeasts
<i>STAT1</i> (2q)	Broadly expressed	614162	AD (GOF)	CMC (>95%), invasive candidiasis (~5%), aspergillosis (~5%), mucormycosis (rare), skin fusariosis (rare), cryptococcosis (rare), histoplasmosis (~5-10%), coccidioidomycosis (~5%), PJP (rare)	Bacterial, NTM, and viral infections, autoimmunity (thyroiditis, T1D, cytopenias, hepatitis), aneurysms, carcinomas	Genetic sequencing	Decreased peripheral blood T _H 17 cells and decreased IL-17 generation by PBMC associated with increased cellular responses to IFN α/β , IFN γ , and IL-27
<i>STAT3</i> (17q)	Broadly expressed	147060 (AD-HIES, Job's syndrome)	AD (DN)	CMC (~80%), nail dermatophytosis, aspergillosis (~25%), scedosporiosis, cryptococcosis, histoplasmosis, GI tract coccidioidomycosis (rare), skin fusariosis (rare), PJP (rare)	Skin staphylococcal infections, bacterial pneumonias, eczema, pneumatocoles, aneurysms, skeletal abnormalities, elevated IgE	Genetic sequencing	Decreased peripheral blood T _H 17 cells

<i>IL12RB1</i> (19p)	Lymphoid and myeloid cells	614891 (MSMD)	AR (LOF)	CMC (~25%), cryptococcosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis	<i>Salmonella</i> and NTM infections	Genetic sequencing, cell surface IL-12Rβ1 expression ^b	Impaired T _H 17 cell differentiation, impaired IL-12– and IL-23–dependent IFNγ generation
<i>CD40L</i> (Xq)	T lymphocytes	308230 (HIGM)	X-linked (LOF)	CMC (5-10%), cryptococcosis, histoplasmosis, PJP	Bacterial, NTM, and parasitic infections, IBD	Genetic sequencing, cell surface CD40L expression ^b	Impaired T lymphocyte responses
<i>IL2RG</i> (Xq)	Lymphoid cells and to a lesser extent myeloid cells	300400 (X-linked SCID)	X-linked (LOF)	CMC, PJP	Bacterial and viral infections, failure to thrive, GvHD	Genetic sequencing, NBS	Severe lymphopenia
<i>IL7R</i> (5p)	Variable (lymphoid cells and to a lesser extent myeloid cells)	608971 (AR-SCID)	AR (LOF)	CMC, PJP	Bacterial and viral infections, failure to thrive, GvHD	Genetic sequencing, NBS, ADA levels	Severe lymphopenia
<i>RAG1</i> (11p)		601457 (AR-SCID)					
<i>RAG2</i> (11p)		601457 (AR-SCID)					
<i>JAK3</i> (19p)		600802 (AR-SCID)					
<i>ADA</i> (20q)		102700 (AR-SCID)					
<i>ZAP70</i> (2q)		269840 (AR-SCID)					
<i>DCLRE1C</i> [ARTEMIS] (10p)		602450 (AR-SCID)					
<i>IKBKG</i> (Xq)	Broadly expressed	300291 (EDA-ID, HIGM)	X-linked (LOF)	CMC (~10%), PJP (~10%)	Bacterial (sinopulmonary), NTM, and viral infections, anhidrotic ectodermal dysplasia	Genetic sequencing	Severe lymphopenia
<i>NFKB1A</i> [IKBA] (14q)	Broadly expressed	612132 (EDA-ID, HIGM)	AD (HI)	CMC (100%), PJP (~60%)	Bacterial (sinopulmonary) and NTM infections,	Genetic sequencing	Severe lymphopenia, decreased peripheral blood T _H 17 cells

					anhidrotic ectodermal dysplasia, IBD		
<i>IL21R</i> (16p)	Lymphocytes and DCs	615207	AR (LOF)	CMC (~25%), invasive candidiasis (~15%), PJP (~35%)	Bacterial and viral infections, gastritis, bronchiectasis, cryptosporidiosis with associated cholangitis and liver cirrhosis	Genetic sequencing	Impaired T lymphocyte activation
<i>CLEC7A</i> [dectin 1] (12p)	Myeloid phagocytes and to a lesser extent epithelial cells	613108	AR (LOF)	Vaginal candidiasis, onychomycosis, disseminated coccidioidomycosis, phaeohyphomycosis	None	Genetic sequencing	Decreased IL-17 generation by PBMC, impaired IL-1 β and TNF- α mediated fungal killing by macrophages
<i>Inborn errors of immunity that manifest with mucocutaneous fungal infections</i>							
<i>IL17RA</i> (22q)	Myeloid cells and epithelial cells	613953	AR (LOF)	CMC (100%)	Skin staphylococcal infections, bacterial pneumonias, eczema	Genetic sequencing	Abolished IL-17 cellular responses
<i>IL17RC</i> (3p)	Epithelial cells	616445	AR (LOF)	CMC (100%)	None	Genetic sequencing	Abolished IL-17 cellular responses
<i>IL17F</i> (6p)	Innate and adaptive lymphoid cells	613956	AD (DN)	CMC (~65%)	Asthma	Genetic sequencing	Impaired IL-17A/F- and IL-17F-dependent cellular responses
<i>TRAF3IP2</i> [ACT1] (6q)	Broadly expressed	615527	AR (LOF)	CMC (100%)	Skin staphylococcal infections, bacterial pneumonias, eczema	Genetic sequencing	Abolished IL-17 cellular responses
<i>IL12B</i> [IL12p40] (5q)	Mononuclear phagocytes	614890 (MSMD)	AR (LOF)	CMC (~5-10%)	<i>Salmonella</i> and NTM infections	Genetic sequencing	Impaired T _H 17 cell differentiation
<i>RORC</i> [ROR γ t] (1q)	Lymphoid cells and epithelial cells	616622	AR (LOF)	CMC (~85%)	NTM infections	Genetic sequencing	Impaired T _H 17 cell differentiation
<i>MAPK8</i> [JNK1] (10q)	Broadly expressed	ND	AD (HI)	CMC (100%)	Bacterial skin infections, UTI, Ehlers-Danlos syndrome	Genetic sequencing	Decreased peripheral blood T _H 17 cells, impaired IL-17 cellular responses

<i>ZNF341</i> (20q)	Broadly expressed	618282 (AR-HIES)	AR (LOF)	CMC (~65%)	Skin staphylococcal infections, bacterial pneumonias, eczema, pneumatoceles, skeletal abnormalities, elevated IgE	Genetic sequencing	Decreased peripheral blood T _H 17 cells
<i>MALTI</i> (18q)	Broadly expressed	615468	AR (LOF)	CMC (~60%)	Bacterial and viral infections, hypogammaglobulinemia, bronchiectasis	Genetic sequencing	Decreased peripheral blood T _H 17 cells, impaired T lymphocyte activation
<i>BCL10</i> (1p)	Broadly expressed	616098	AR (LOF)	CMC (~30%)	Bacterial, NTM, and viral infections, gastrointestinal infections, hypogammaglobulinemia	Genetic sequencing	Unknown
<i>IRF8</i> (16q)	DCs and to a lesser extent lymphocytes	226990 (MSMD)	AR (LOF)	CMC (~15%)	NTM and viral infections	Genetic sequencing	Decreased peripheral blood T _H 17 cells
<i>STK4</i> (20q)	Lymphoid and myeloid cells	614868	AR (LOF)	CMC (ND)	Bacterial and viral infections, warts, lymphoproliferative disorders, neutropenia, cardiac malformations	Genetic sequencing	Unknown
<i>AIRE</i> (21q)	mTECs and eTACs	240300 (APECED, APS-1)	AR (LOF) or AD (DN)	CMC (~85%)	Multiorgan autoimmune manifestations (hypoparathyroidism, adrenal insufficiency, thyroiditis, T1D, hypogonadism, pneumonitis, enteropathy, asplenia, hepatitis, gastritis), ectodermal dystrophy, severe COVID-19	Genetic sequencing, AAbs to IFN α and IFN ω	Neutralizing serum AAbs against IL-17A (~30%), IL-17F (~20-80%), and IL-22 (~80%), decreased generation of <i>Candida</i> -specific T _H 17 cells by mouse eTACs with minimally affected global T _H 17 response, impaired epithelial barrier integrity caused by excessive IFN γ generation by mucosal T lymphocytes

					pneumonia, herpetic infections (~10%)		
<i>DOCK8</i> (9p)	Broadly expressed	243700 (AR-HIES)	AR (LOF)	CMC (~60%)	Viral skin infections, eczema, carcinomas, elevated IgE	Genetic sequencing	Impaired T _H 17 cell differentiation
<i>ISG15</i> (1p)	Broadly expressed	616126 (MSMD)	AR (LOF)	Skin aspergillosis (rare)	NTM infections, necrotizing skin inflammation, CNS calcifications	Genetic sequencing	Unknown
<i>IKZF2</i> (2q)	Broadly expressed	ND	AR (LOF) or AD (DN)	CMC (~65%)	Respiratory infections, oral ulcers, lichen planus, thyroiditis, vitiligo, lymphoma	Genetic sequencing	Unknown (normal T _H 17 cells, increased IFN γ generation by T lymphocytes, decreased MAIT cells)
<i>ELF4</i> (Xq)	Broadly expressed	301074	X-linked (LOF)	CMC (~25%)	Bacterial and viral respiratory infections, oral ulcers, gastritis, IBD	Genetic sequencing	Unknown (increased T _H 17 cells, enhanced interferon responses)
21q22.3	N/A	190685 (Down syndrome, trisomy 21)	N/A	CMC (~65%)	Autoimmunity, hypothyroidism, congenital cardiac and gastrointestinal defects, mental retardation, leukaemia, early-onset Alzheimer's disease	Genetic sequencing, prenatal screening	Unknown (normal T _H 17 cells, enhanced IFN γ cellular responses)
<i>Inborn errors of immunity that manifest with invasive fungal infections</i>							
<i>CYBB</i> /gp91 ^{phox} (Xp)	Myeloid phagocytes	306400 (X-linked CGD)	X-linked (LOF)	Aspergillosis (~40%), invasive candidiasis (<5%)	Invasive infections by <i>Nocardia</i> , <i>Staphylococcus</i> , <i>Serratia</i> , and <i>Burkholderia</i> , IBD	Genetic sequencing, DHR testing	Impaired generation of superoxide
<i>CYBA</i> [p22 ^{phox}] (16q)	Myeloid phagocytes	233690 (AR-CGD)	AR (LOF)	Aspergillosis (~40%), invasive candidiasis (<5%)	Invasive infections by <i>Nocardia</i> , <i>Staphylococcus</i> ,	Genetic sequencing, DHR testing	Impaired generation of superoxide
<i>NCF1</i> [p47 ^{phox}] (7q)		233700 (AR-CGD)					

<i>NCF2</i> [p67 ^{phox}] (1q)		233710 (AR-CGD)			<i>Serratia</i> , and <i>Burkholderia</i> , IBD		
<i>CYBC1</i> [EROS] (17q)	Myeloid phagocytes and to a lesser extent lymphocytes	618935 (AR-CGD)	AR (LOF)	Invasive candidiasis (<10%)	Invasive <i>Burkholderia</i> , <i>Legionella</i> and pneumococcal infections, herpetic infections, AIHA, ILD, IBD	Genetic sequencing, DHR testing	Decreased expression of gp91 ^{phox} , impaired generation of superoxide
<i>NCF4</i> [p40 ^{phox}] (22q)	Myeloid phagocytes	613960 (AR-CGD)	AR (LOF)	Histoplasmosis (rare)	Staphylococcal skin infections, bacterial pneumonias, discoid lupus, periodontitis, ILD, IBD	Genetic sequencing, DHR testing	Impaired generation of superoxide in neutrophils (preserved in mononuclear phagocytes)
<i>PRKCD</i> [PKD- δ] (3p)	Broadly expressed	615559	AR (LOF)	Invasive candidiasis (<10%)	Staphylococcal, <i>Legionella</i> and pneumococcal infections, pneumonias, gastroenteritis, herpetic infections, AIHA, lupus	Genetic sequencing	Decreased activation of p40 ^{phox} , impaired generation of superoxide
MPO (17q)	Myeloid phagocytes	254600	AR (LOF)	Invasive candidiasis (<5%)	None	Genetic sequencing, MPO staining by FACS or IHC	Impaired generation of hypochlorous acid
<i>ELANE</i> (19p)	Myeloid phagocytes	202700 (SCN)	AD (DN)	Invasive candidiasis (rare), aspergillosis (rare)	Bacterial infections, AML/MDS, osteopenia, periodontitis	Genetic sequencing	Neutropenia
<i>HAX1</i> (1q)	Broadly expressed	610738 (SCN)	AR (LOF)	Invasive candidiasis (rare), aspergillosis (rare)	Bacterial infections, AML/MDS, neurological abnormalities, periodontitis	Genetic sequencing	Neutropenia

<i>JAGNI</i> (3p)	Broadly expressed	616022 (SCN)	AR (LOF)	Invasive candidiasis (rare)	Bacterial infections, short stature, teeth, and bone defects, periodontitis	Genetic sequencing	Neutropenia, impaired neutrophil fungicidal activity
<i>VPS45</i> (1q)	Broadly expressed	615285 (SCN)	AR (LOF)	Aspergillosis (~10-20%)	Bacterial infections, myelofibrosis, nephromegaly, periodontitis	Genetic sequencing	Neutropenia, impaired cell migration
<i>ITGB2</i> [CD18] (21q)	Myeloid phagocytes and to a lesser extent lymphocytes	116920 (LAD)	AR (LOF)	Invasive candidiasis (rare), aspergillosis (rare)	Severe periodontitis, IBD, impaired wound healing	Genetic sequencing, cell surface CD18 expression ^b	Impaired trafficking of neutrophils to infected tissues
<i>CTSC</i> (11q)	Broadly expressed	245000 (Papillon-Lefevre syndrome)	AR (LOF)	Mucormycosis (rare)	Bacterial infections, severe periodontitis, palmoplantar keratoderma	Genetic sequencing	Impaired activation of granule serine proteases
<i>CSF2RA</i> (Xp)	Myeloid phagocytes and epithelial cells	300770	X-linked (LOF)	Cryptococcosis and aspergillosis (~5%)	PAP, bacterial, NTM, and <i>Nocardia</i> pulmonary infections	Genetic sequencing	Impaired GM-CSF cellular responses
<i>CSF2RB</i> (22q)	Myeloid phagocytes, lymphocytes, and epithelial cells	614370	AR (LOF)	Cryptococcosis and aspergillosis (~5%)	PAP, bacterial, NTM, and <i>Nocardia</i> pulmonary infections	Genetic sequencing	Impaired GM-CSF cellular responses
<i>IFNGR1</i> (6q)	Broadly expressed	209950 (AR-MSMD)	AR (LOF)	Histoplasmosis (rare), coccidioidomycosis (rare)	<i>Salmonella</i> and NTM infections	Genetic sequencing, cell surface IFNGR1 expression ^b	Impaired IFN γ cellular responses
		615978 (AD-MSMD)	AD (DN)				
<i>STAT3</i> (17q)	Broadly expressed	ND	AD (HI)	Sino-orbital aspergillosis	Allergic rhinitis	Genetic sequencing	Unknown
<i>STAT4</i> (2q)	Lymphoid cells and DCs	ND	AD (DN)	paracoccidioidomycosis	None	Genetic sequencing	Impaired IL-12–dependent IFN γ generation, impaired macrophage fungicidal activity

<i>GATA2</i> (3q)	Neutrophils and to a lesser extent mononuclear phagocytes and T lymphocytes	614172 (MonoMAC syndrome, Emberger syndrome)	AD (HI)	Aspergillosis (~10%), cryptococcosis (~5%), histoplasmosis (~5%), coccidioidomycosis (rare), blastomycosis (rare), PJP (rare)	Viral and NTM infections, PAP, MDS, leukaemia, lymphedema	Genetic sequencing, bone marrow examination	Decreased monocyte and DC counts, neutrophil granule abnormalities
<i>IKZF1</i> (7p)	Myeloid and lymphoid cells	616873	AD (HI or DN)	PJP (~20%), aspergillosis (~10%)	Bacterial sinopulmonary and CNS infections, herpetic and NTM infections, leukaemia, autoimmune manifestations (ITP, AIHA, lupus), hypogammaglobulinemia	Genetic sequencing	Neutropenia, impaired T lymphocyte proliferation and memory phenotype acquisition
<i>IKZF3</i> (17q)	Lymphoid cells and DCs	619437	AD (DN)	PJP (~50%)	Sinopulmonary infections, hypogammaglobulinemia, bronchiectasis, NTM infections, warts, leukaemia, lymphoma	Genetic sequencing	Impaired CD40L expression on T lymphocytes, impaired Th1 differentiation
<i>BTK</i> (Xq)	B cells and myeloid phagocytes	300755 (XLA)	X-linked	PJP (rare), cryptococcosis (rare), aspergillosis (rare)	Bacterial infections, agammaglobulinemia IBD	Genetic sequencing	Impaired B lymphocyte signaling

^aOMIM, Online Mendelian Inheritance in Man. ^bBy fluorescence-activated cell sorting. AD, autosomal dominant; AIHA, autoimmune hemolytic anemia; AIRE, autoimmune regulator; AML, acute myelogenous leukaemia; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS-1, autoimmune polyglandular syndrome type-1; AR, autosomal recessive; BCL10, B-cell lymphoma/leukaemia 10; BTK, Bruton's tyrosine kinase; CARD9, Caspase recruitment domain-containing protein 9; CGD, chronic granulomatous disease; CMC, chronic mucocutaneous candidiasis; CNS, central nervous system; COVID-19, coronavirus disease 2019; CSF2R, colony stimulating factor 2 receptor; CTSC, cathepsin C; CYB, cytochrome b-245; CYCB1, cytochrome b-245 chaperone 1; DCLRE1C, DNA cross-link repair 1C; DCs, dendritic cells; DHR, dihydrorhodamine; DN, dominant negative; DOCK8, dedicator of cytokinesis 8; ELANE, elastase, neutrophil expressed; ELF4, E74 like ETS transcription factor 4; EDA-ID, anhidrotic ectodermal dysplasia with immune deficiency; eTACs, extrathymic AIRE-expressing cells; FACS, fluorescence-activated cell sorting; GM-CSF, granulocyte macrophage-colony stimulating factor; GOF, gain of function; GvHD, graft-versus-host disease; HAX1, HCLS1 associated protein X-1; HI, haploinsufficiency; HIES, hyper-IgE syndrome; HIGM, hyper-IgM syndrome; IBD, inflammatory bowel disease; IFN, interferon; IHC, immunohistochemistry; IKBKG, inhibitor of NF-κB kinase regulatory subunit gamma; IKZF, IKAROS family zinc finger; ILD, interstitial lung disease; IP, incomplete penetrance; IRF8, interferon regulatory factor 8; ISG15, interferon-stimulated gene 15; ITP, immune thrombocytopenic purpura; JAGN1,

Jagunal homolog 1; JAK, Janus kinase; LAD, leukocyte adhesion deficiency; LOF, loss of function; MAIT, Mucosal-associated invariant T; MALT1, mucosa-associated lymphoid tissue lymphoma translocation 1; MAPK8, mitogen-activated protein kinase 8; MDS, myelodysplastic syndrome; MPO, myeloperoxidase; MSMD, mendelian susceptibility to mycobacterial disease; mTECs, medullary thymic epithelial cells; N/A, not applicable; NBS, newborn screening; NCF, neutrophil cytosolic factor; ND, not defined; NFKBIA, NF- κ B inhibitor alpha; NTM, non-tuberculous mycobacteria; OMIM, online mendelian inheritance in man; PAP, pulmonary alveolar proteinosis; PBMC, peripheral blood mononuclear cells; PJP, *Pneumocystis jirovecii* pneumonia; PRKCD, protein kinase C delta; RAG, recombination activating gene; SCID, severe combined immunodeficiency; RORC, RAR related orphan receptor C; SCN, severe congenital neutropenia; STAT, signal transducer and activator of transcription; STK4, serine/threonine kinase 4; T1D, type 1 diabetes; T_H17, T helper 17; TRAF3IP2, TRAF3 interacting protein 2; UTI, urinary tract infection; VPS45, vacuolar protein sorting 45 homolog; XLA, X-linked agammaglobulinemia; ZAP70, zeta chain of T cell receptor associated protein kinase; ZNF341, zinc finger protein 341.

Supplementary Table 3 | Key FDA-approved immune-targeted biologics associated with the development of human fungal infections

Molecular target	Name of biologic	Type of biologic	Approved indications	Fungal infection susceptibility	Risk of fungal infection (mean frequency, when known)	Non-fungal infection susceptibility	Antifungal immunological defects (when known)
<i>Biologics that promote the development of both mucocutaneous and invasive fungal infections</i>							
TNF	Infliximab	Mouse-human chimeric IgG1k mAb	RA, AS, psoriasis, IBD	Histoplasmosis, coccidioidomycosis, blastomycosis, PJP	Moderate/high	Mycobacterial infections (including disseminated TB)	Impaired IFN γ generation and granuloma formation; impaired phagocyte trafficking and function
	Etanercept	p75 TNF- α soluble receptors fused to the Fc portion of IgG1					
	Adalimumab	Humanized IgG1k mAb		Mucosal candidiasis, invasive candidiasis, aspergillosis, phaeohyphomycosis	Low (<5%)		
	Golimumab	Humanized IgG1k mAb					
CD52	Alemtuzumab	Humanized IgG1k mAb	MS, CLL	Cryptococcosis, PJP, mucosal candidiasis	Moderate/high	Herpetic infections, CMV reactivation, toxoplasmosis, nocardiosis, bacterial pneumonia	Prolonged and profound T lymphocytopenia
C-RAF/B-RAF	Sorafenib	Dual kinase inhibitor	RCC, HCC	Aspergillosis, mucosal candidiasis, skin fungal infection	Low	Bacterial pneumonia	Impaired ERK signaling Impaired T lymphocyte responses
<i>Biologics that promote the development of mucocutaneous fungal infections</i>							
IL-17A	Ixekizumab	Humanized IgG4 mAb	Psoriasis, AS, IBD	Mucosal candidiasis	Low/moderate (~2-12% depending on the biologic)	None	Impaired IL-17 cellular responses
	Secukinumab	Humanized IgG1k mAb					
IL-17RA	Brodalumab	Humanized IgG2 mAb					
IL-12p40	Ustekinumab	Humanized IgG1k mAb					
IL-23p19	Risankizumab	Humanized IgG1k mAb					
	Guselkumab	Humanized IgG1 λ mAb					
	Tildrakizumab	Humanized IgG1k mAb					
SYK	Fostamatinib	Kinase inhibitor	ITP	Vaginal candidiasis, skin fungal infection	Low/moderate (up to ~10%)	Upper respiratory infections	Impaired IL-17 cellular responses

Biologics that promote the development of invasive fungal infections							
JAK1/2/3	Ruxolitinib, tofacitinib, baricitinib, upadacitinib, fedratinib	Kinase inhibitors	MF, PV, GvHD, RA, IBD	Histoplasmosis, coccidioidomycosis, cryptococcosis, talaromycosis, PJP, aspergillosis	Moderate/high	Herpetic, CMV, and mycobacterial infections	Impaired IFN γ and IFN λ cellular responses, impaired lymphocyte and monocyte/macrophage activation, lymphocytopenia
IFN γ	Emapalumab	Humanized IgG1 mAb	HLH	Histoplasmosis, coccidioidomycosis, PJP	Moderate/high	Viral, bacterial, and mycobacterial infections	Impaired IFN γ cellular responses
BTK	Ibrutinib, acalabrutinib, zanubrutinib	Kinase inhibitors	CLL, MZL, MCL, WM, GvHD	Aspergillosis (with CNS involvement), mucormycosis, fusariosis, cryptococcosis, histoplasmosis, blastomycosis, PJP	Moderate/high	Viral and bacterial infections	Impaired myeloid phagocyte activation and function
BCL-2	Venetoclax	BH3-mimetic	AML, CLL	Invasive candidiasis, aspergillosis, PJP	Low	Bacterial infections	Unknown
C5a	Eculizumab	Humanized IgG2/4k mAb	PNH, HUS	Invasive candidiasis, aspergillosis	Moderate (up to ~10%)	Infections by encapsulated bacteria	Impaired myeloid phagocyte activation and function
CD20	Rituximab	Mouse-human chimeric IgG1k mAb	RA, CLL, lymphomas	PJP	Low	Bacterial infections, PML	B lymphocytopenia and impaired T lymphocyte responses against <i>Pneumocystis</i>
IL-6R	Tocilizumab	Humanized IgG1k mAb	RA, CRS after CAR T cells	Invasive candidiasis, cryptococcosis, coccidioidomycosis, PJP	Low	Bacterial infections	Impaired myeloid phagocyte trafficking and activation
S1PR	Fingolimod	Aminodiol	MS	Cryptococcosis	Low	Herpetic and respiratory infections	Impaired T macrophage phagocytosis and killing, and defective granuloma formation

PI3K (p110δ)	Idelalisib	Kinase inhibitor	CLL, lymphomas	PJP	Moderate (~5-10%)	CMV infections, bacterial pneumonia	Impaired T lymphocyte activation
BCR/ABL	Dasatinib	Kinase inhibitor	CML	PJP	Low/moderate	Herpetetic and CMV infections, hepatitis B reactivation	Impaired T lymphocyte activation
α4 integrin	Natalizumab	Humanized IgG4k mAb	MS	Cryptococcosis	Low	PML	Impaired T lymphocyte trafficking
CTLA-4	Abatacept	Chimeric CTLA4 and IgG1 Fc fusion protein	RA	Invasive candidiasis, aspergillosis, histoplasmosis, PJP	Low	Bacterial infections	Impaired CD80/CD86:CD28 co-stimulation and T lymphocyte activation
VEGF	Bevacizumab	Humanized IgG1 mAb	Colorectal, lung, and cervical cancer	Aspergillosis, fusariosis, PJP	Low	Bacterial infections	Unknown

AML, acute myelogenous leukaemia; AS, ankylosing spondylitis; BCL-2, B cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukaemia; CML, chronic myelogenous leukaemia; CMV, cytomegalovirus; CNS, central nervous system; CRS, cytokine release syndrome; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ERK, extracellular *signal*-regulated kinase; GvHD, graft-versus-host disease; HCC, hepatocellular carcinoma; HLH, *hemophagocytic lymphohistiocytosis*; HUS, hemolytic uremic syndrome; IBD, inflammatory bowel disease; IFN, interferon; ITP, immune thrombocytopenic purpura; JAK, Janus kinase; mAb, monoclonal antibody; MCL, mantle cell lymphoma; MF, myelofibrosis; MS, multiple sclerosis; MZL, marginal zone lymphoma; PI3K, phosphoinositide 3-kinase; PJP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; PNH, paroxysmal nocturnal hemoglobinuria; PV, polycythemia vera; RA, rheumatoid arthritis; RAF, rapidly accelerated fibrosarcoma; RCC, renal cell carcinoma; S1PR, sphingosine 1 phosphate receptor; SYK, spleen tyrosine kinase; TB, tuberculosis; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; WM, Waldenström's macroglobulinemia.