Allergen Extract Cross-reactivity

ALK TECHNICAL MEMO
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ALK entered the US allergenic extract market in 1985 after more than 50 years of success in Europe. Since that time, ALK has grown to be one of the top US extract suppliers, providing consistent, quality products to numerous markets for allergy testing and treatment. Allergen cross-reactivity is a central focus in the allergy field that can be utilized to optimize allergy testing and treatment panels and substitutes when inventory is unavailable. This technical memo is intended to provide guidelines for the selection of immunotherapy extracts based on knowledge of allergen and epitope cross-reactivity. Medical Scientific Affairs is available to personally assist your practice and answer cross-reactivity questions as they arise.

Cross-reactivity Definition

The term *cross-reactivity* refers to 2 distinct antigens that are recognized by the same antibody and elicit the same immune response. Cross-reactivity in allergic reactions occurs when the proteins from 1 allergenic species produce an allergic response to a similar protein from another species.[1] This phenomenon occurs between different types of pollens, foods, epidermals, and insect allergens and is the basis for oral allergy syndrome. In the clinical setting, cross-reactivity can complicate the diagnosis of specific allergies, especially in patients who frequently travel.[2] Clinically, allergic cross-reactivity is often encountered as symptoms without prior exposure.[3]

The similarity of the amino acid sequences and 3-dimensional structures of protein dictate cross reactivity. Allergenic species that are closely related by biological taxonomy have similar allergenic protein structures. Species of the same taxonomic genus and family exhibit as much as 70%-90% amino acid sequence homology and shared common IgE epitopes. Conversely, the greater the taxonomic distance between allergenic species, the less cross-reactive their proteins are, due to less conserved protein homology and lower affinity (binding) by IgE.

The scientific literature supporting allergen cross reactivity is largely based on clinical studies and biological taxonomy. While IgE-binding inhibition studies have been performed to demonstrate cross-reactivity for some species, most evidence stems from percutaneous or serum IgE tests. Taken together, these reports establish general patterns for cross-reactivity: species within the same genus are expected to be highly cross-reactive, while members of the same family are likely to be moderately cross-reactive. As species become more distantly related (by order, class, etc), the likelihood of protein cross-reactivity declines accordingly (Figure 1). For example, individual species of the birch genus, *Betula*, have been shown to be highly cross-reactive, and protein homology is strongly conserved among this genus.[2] The *Betula* genus belongs to the *Betulacea* family, which also includes alders, shown to exhibit moderate cross-reactivity with birch trees. Further, the birch (*Betulacea*) family is within the beech order *Fagales*, which contains oak trees, and studies suggest that birch and oak allergy is related with the pollen exposure driving cross-sensitization with these allergens.[4] However, it is important to note that other members of the *Fagales* order, such as species within the genus *Betula* and *Juglandaceae*, do not strongly cross-react. In general, extensive cross-reactivity among the different individual species of a genus is expected, as well as to a certain degree among members of a family. Awareness of these taxonomic and cross-reactive relationships among allergenic species is important to achieve appropriate dosing and enables the identification of appropriate allergen substitutes.

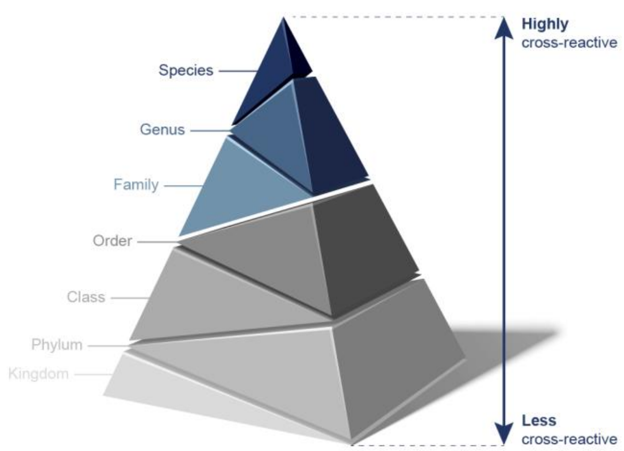

Figure 1. When pollens are substantially cross-reactive, selection of a single pollen within the cross-reactive genus or family might suffice. When pollen allergens are not substantially cross-reactive (order, class, phylum), testing for and treatment with multiple locally prevalent pollens might be necessary.[6]

Importance of Cross-reactivity

Knowledge of cross-reactivity is important for 2 primary reasons for diagnosing and treating patients with immunotherapy:

1. Not all species of allergenic material a patient is exposed to is present in the portfolios of the allergen manufacturers
2. Awareness of similar cross-reactive proteins is necessary in order to achieve proper dosing for both safety and efficacy

A key part of testing and treating allergies by immunotherapy is selection of the appropriate allergens for screening. Many factors are involved in choosing the appropriate species, such as geographical region, relevance of offending allergens, and availability/cost of the extracts. Similarity of allergens can help optimize panels. For reducing the number of allergens, cross-reactivity can be useful. When determining dosing strategies, the presence of cross-reactive allergens should be considered.

Types of Cross-reactivity

Major Allergen

The term *major allergen* is given to any allergenic protein to which more than 50% of the allergen-sensitized population react.[4] These protein are generally well conserved across species in the same genus and family. For example, the northern pasture grasses all express the major allergen Phl p 5, a cytoplasmic starch particle. As a consequence, these grasses are all highly cross-reactive, and often a single species from this group is sufficient to treat reactivity to all.[5]

Panallergens

Some allergenic proteins are conserved across a wide range of species and are referred to as *panallergens*. These are protein present in pollen or food that are genetically well conserved across a wide range of taxonomic species. The most notable panallergen is profilin, which is an actin-binding protein present in trees, weeds, and grasses.[6] Profilin-sensitive patients often react to numerous allergens on a testing panel and can be misdiagnosed as polysensitized. To discriminate profilin allergy, component testing for profilin or allergy testing for Queen Palm (a pollen that contains a high concentration of profilin) is often utilized. Panallergens also exist in animal extracts, as albumins and lipocalins of epithelium and danders.

Oral Allergy Syndrome

Another notable exception to the taxonomic relationships of cross-reactivity occur in the unique food allergy known as oral allergy syndrome (OAS).[7] OAS accounts for nearly 30% of adult oral food allergies and is thought to be caused by an IgE-driven cross-reactivity between food protein and a prior aeroallergen sensitization.[8] In these cases, patients are often sensitized to pathogen response (PR) proteins, which are naturally occurring plant protein designed to respond to fungal or bacterial infection and very well conserved across plant taxonomy. One of the best examples of PR cross-reactivity is that of birch pollen and the foods apple, potato, and hazelnut; this cross-reactivity is attributed to the birch major allergen Bet v 1, also known as PR-10, which is present in all 4 species.[9]

Formulation Considerations

A key facet of allergy testing is determining relevant allergens for screening. Many factors are involved in choosing the appropriate species, including geographical region, prevalence of offending allergens, and availability/cost of the extracts. To best optimize an allergen-testing panel, it's important to have an understanding of the cross-reactivity of allergens within it. According to the practice parameters, "When preparing mixtures of allergen ex- tracts, the prescribing physician must take into account the cross-reactivity of allergen extracts and the potential for allergen degradation caused by proteolytic enzymes."[6] Not all allergenic species in the environment are present in the product portfolios of extract manufacturers, so anticipating cross-reactive relationships enables the selection of appropriate allergens to maximize your panel's relevance. Consider the necessity of including multiple cross-reactive species on a panel, especially when the species reside in the same taxonomic family. Often these groups of pollens can be trimmed to 1 representative species, which frees up space for other allergens and/or reduces the number of skin prick tests a patient receives.

When prescribing immunotherapy for an allergic patient, cross-reactivity should be considered during treatment formulation. Awareness of cross-reactivity among species within the immunotherapy vial is necessary to achieve appropriate dosing, as adding too many allergens to a treatment vial can dilute and decrease overall therapeutic efficacy. On the other hand, adding too much cross-reactive allergen can lead to an adverse reaction and otherwise avoidable dilutions.[4] It is also important to note that IgE reactivity can produce sensitization to other species to which the patient was not exposed. This concept should be kept in mind as allergic individuals often travel and relocate across the globe.[3]

Taxonomic Allergen Tables

Below you will find tables of the biological taxonomic organization of pollen and fungal species commonly considered to be allergen sources in North America. Where data are lacking for clinical cross reactivity, it is useful to associate the similarity to be strong within a genus. In general, as the taxonomic relationship moves to family and order, there is reduced cross-reactivity, though this varies depending on the order and class.

ALK Commitment

ALK is committed to helping allergy specialists maintain uniformity of care for their patients. Please do not hesitate to contact Medical Scientific Affairs (855.782.9323, science@alk.net, or submit your scientific questions to our 24/7 online helpdesk in a support ticket at: https://alkinc.freshdesk.com) should you have additional questions or concerns regarding ALK products.

References

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Mold Cross-Reactivity

PHYLUM	CLASS	ORDER	FAMILY	GENUS
Ascomycota	Dothideomycetes	Pleosporales	Pleosporaceae	**Alternaria**
				Curvularia
				Bipolaris / Drechlera
				Helminthosporium
				Stemphilium
			Incertæ sedis	**Epicoccum**
				Phoma
		Capnodiales	Davidiellaceae	**Cladosporium**
		Dothideales	Dothioraceae	**Aureobasidium**
	Eurotiomycetes	Eurotiales	Trichocomaceae	**Aspergillus**
				Pennicilium
		Onygenales	Arthrodermataceae	Trichophyton
	Sordariomycetes	Hypocreales	Nectriaceae	**Fusarium/Gibberella**
			Hypocreaceae	**Trichoderma**
				Acremonium/ Sarocladium
			Stachybotryaceae	Stachybotrys
		Sordariales	Sordariaceae	Neurospora
			Chaetomiaceae	Chaetomium
		Trichosphaeriales	Trichosphaeriaceae	Nigrospora
	Leotiomycxetes	Heliotiales	Sclerotiniaceae	**Botrytis**
	Saccharomycetes	Saccharomycetales	Saccharomycetaceae	**Candida**
				Saccharomyces
			Dipodascaceae	Geotrichum
Zygomycota	Mucoromycotina	Mucorales	Mucoraceae	**Mucor**
				Rhizopus
Basidiomycota	Microbotryomycetes	Sporidiobolales	Incertæ sedis	**Rhodotorula**
	Ustilaginomycetes	Ustilaginales	Ustilaginaceae	Ustilago
	Exobasidiomycetes	Malasseziales	Malasseziaceae	Malassezia
	Agaricomycetes	Agaricales	Hymenogastraceae	Psilocybe

Bold = ALK Extract Available

Mold containing the same genus name (e.g. Aspergillus niger and Aspergillus fumigatus) are considered cross-reactive, and these molds can be readily substituted for one another. Additional cross-reactivity considerations may apply. In recent publications cross-reactivity has been suggested to occur among mold contained within the same Order, Class, or Phylum.

Grass Cross-Reactivity

CLASS	ORDER	FAMILY	SUBFAMILY	TRIBE	GENUS	SPECIES
Commelinids	Poales	Poacea	Chloridoideae	Aeluropidea	Distichlis	Saltgrass
				Sporoboleae	Sporobolus	Dropseed
				Chlorodiea	Cynodon	**Bermuda**
					Bouteloua	Grama, Buffalo
				Eragrostideae	Eragrostis	Lovegrass
			Arundinocideae	Arundineae	Arundo	Giant reed
					Phragmites	Common reed
			Panicodieae	Andropogoneae	Sorghum	**Johnson Grass**
					Zea	Corn
					Saccharum	Sugar cane
				Paniceae	Digitaria	Crabgrass
					Paspalum	**Bahia**
					Axonopus, Stenotaphrum	Carpetgrass,St Augustine
			Pooideae (Temperate or Northern Pasture)	Poeae (Festuceae)	Dactylis	**Orchard**
					Festuca	**Meadow Fescue**
					Lolium	**Ryegrass, Perennial**
					Poa	**June (Kentucky Bluegrass)**
					Bromus	**Brome**
				Aveneae	Holcus	Velvet grass
					Avena/Arrhenatherum	Oat
				Agrostideae	Phleum	**Timothy**
					Agrostis	**Redtop**, Bent grass
					Alopecurus	Foxtail
				Phalarideae	Phalaris	Canary
					Anthoxanthum	**Sweet vernal**
				Triticeae	Triticum	Wheat
					Secale	Rye, Cereal
					Hordeum	Barley
					Elymus	**Quack grass**
			Bambusoideae	Bambuseae	Bambusa	Bamboo
			Oryzoideae	Oryzeae	Oryza	Rice

Bold = ALK Extract Available

If an extract is unavailable, a cross-reactive substitute can be offered. Grass allergens that belong to the same taxonomic sub-family are easily interchangeable. For example Timothy grass is expected to be cross-reactive with Pooideae subfamily, including Orchard, Sweet Vernal, and Perennial Rye grasses.

Weed Cross-Reactivity

CLASS	ORDER	FAMILY	SUBFAMILY	TRIBE	GENUS	SPECIES
Rosids	Brassicales	Brassicaceae (Cruciferae)			Brassica	Oil Rape (Canola), Mustard, Cabbage, papaya
	Fabales	Fabaceae (Leguminosae)			Medicago	**Alfalfa**
					Trifolium	Clover
					Lupinus	Lupine
					Cytisis	Broom
	Rosales	Urticaceae			Urtica	**Nettle**
					Parietaria	Pellitory
Asterids	Asterales	Asteraceae (Compositae)		Anthemideae	Artemeisia	**Mugwort, Sagebrush**
					Mariciaria	Camomile
					Chrysanthemum	Rabbitbrush, Pyrethrum
				Astereae	Solidago	**Goldenrod**
					Baccharis	Groundsel
				Cichorieae	Taraxacum	**Dandelion**
				Eupatorieae	Eupatorium	**Dog fennel**
				Heliantheae	Ambrosia	**Ragweeds**, Rabbitbush **False Ragweed (bur), Short Ragweed, Giant (tall) Ragweed, Western Ragweed**
					Cycachaena	**Marshelder, Burweed**
					Iva	**Marshelder, True (rough)**
					Xanthium	**Cocklebur**
					Helianthus	Sunflower
	Lamiales	Plantaginaceae			Plantago	**English plantain**
Rosids or Asterids (Core Eudicots)	Caryophyllales (Cacti,Succulents)	Amaranthaceae	Betoideae		Amaranthus	**Pigweed, Carelessweed, Water Hemp**
					Beta	Sugar beet
			Salsolooideae		Salsola	**Russian thistle**
			Chenopodioideae		Atriplex	**Lenscales, Saltbush**
					Chenopodium	**Lamb's Quarters (goosefoot)**
			Camphorosmoides		Kochia	**Firebush**
		Polygonaceae			Rumex	**Sheep Sorrel (Sour Dock), Yellow (Curly Dock)**

Bold = ALK Extract Available

Cross-reactivity is important to keep in mind with pollen extracts. If an extract is unavailable, a cross-reactive substitute can be offered. Extensive cross-reactivity among the different individual species of a genus can be expected, as well as to a certain degree among members of a family. For example all Ragweed species (Ambrosia genus) are highly cross-reactive, and exhibit moderate cross-reactivity with other members of the Asteraceae family (e.g Mugwort, Marhshelder, and Cocklebur).

Tree Cross-Reactivity

CLASS	ORDER	FAMILY	SUBFAMILY	TRIBE	GENUS	SPECIES
Rosids	Fabales	Fabaceae (Leguminosae)			Acacia	**Acacia**
					Prosopis	**Honey Mesquite**
					Robina	Black, Honey Locust
	Fagales	Betulaceae			Betula	**Red (River), White, Black-Sweet Birch**
					Alnus	**White, Red Alder**
					Corylus	**Hazelnut**
					Carpinus	Hornbean
		Juglandaceae			Juglans	**Black,** English Walnut
					Carya	**Pecan, Hickory**
		Myricaceae			Morella	**Bayberry (Wax Myrtle)**
		Casuarinaceae			Casuarina	**Australian Pine (Beefwood)**
		Fagaceae			Fagus	**American Beech**
					Castanea	Chestnut
					Quercus	**White, Red, Virginia Live Oak**
	Malpighiales	Saliaceae			Populus	**Eastern (Common), Western,** Fremont Cottonwood, **Poplar, Aspen**
					Salix	**Black Willow**
	Myrtales	Myrtaceae			Eucalyptus	**Eucalyptus globulus, Blue Gum**
					Melaleuca	**Melaleuca**
	Rosales	Cannabaceae (Cannabis Hemp, Hop)			Celtis	**Hackberry**
		Ulmaceae			Ulmus	**American, Chinese (Siberian), Cedar Elm**
		Moraceae			Morus	**White, Red Mulberry**
		Elaeagnaceae			Elaeagnus	Russian Olive
	Sapindales	Aceraceae (Sapindaceae)			Acer	**Red Maple, Sugar Maple, Box Elder**
		Anacardiaceae (Cashew, Mango)			Schinus	**California Pepper Tree**
		Simarobaceae			Ailanthus	Tree of Heaven
		Anacardiaceae			Toxicodendron	Poison Oak, Ivy, Sumac
Asterids	Lamiales	Oleaceae			Olea	**European Olive**
					Ligustrum	**Privet**
					Fraxinus	**White Ash**, Green Ash, **Arizona Ash**
Pinopsida	Pinales	Cupressaceae	Cupressoideae		Juniperus	**Mountain Cedar, Eastern Red Cedar, Western Rocky Mountain Juniper**
					Cupressus	**Arizona Cypress**
			Taxodioideae		Taxodium	**Bald Cypress**
		Pinaceae			Pinus	**White, Yellow Longleaf Pine**
N/A	Proteales	Platanaceae			Platanus	**American,** Western Sycamore (Plane Tree)
	Saxifragales	Atingiaceae			Liquidambar	**Sweet Gum**
Commelinids	Arecales	Arecaceae			Syagrus (Cocos)	**Queen Palm,** Date Palm

Bold = ALK Extract Available

Cross-reactivity is important to keep in mind with pollen extracts. If an extract is unavailable, a cross-reactive substitute can be offered. Extensive cross-reactivity among the different individual species of a genus can be expected, as well as to a certain degree among members of a family. For example members of the Betula genus (e.g. White Birch, Red Birch and Black Birch) are cross-reactive.