

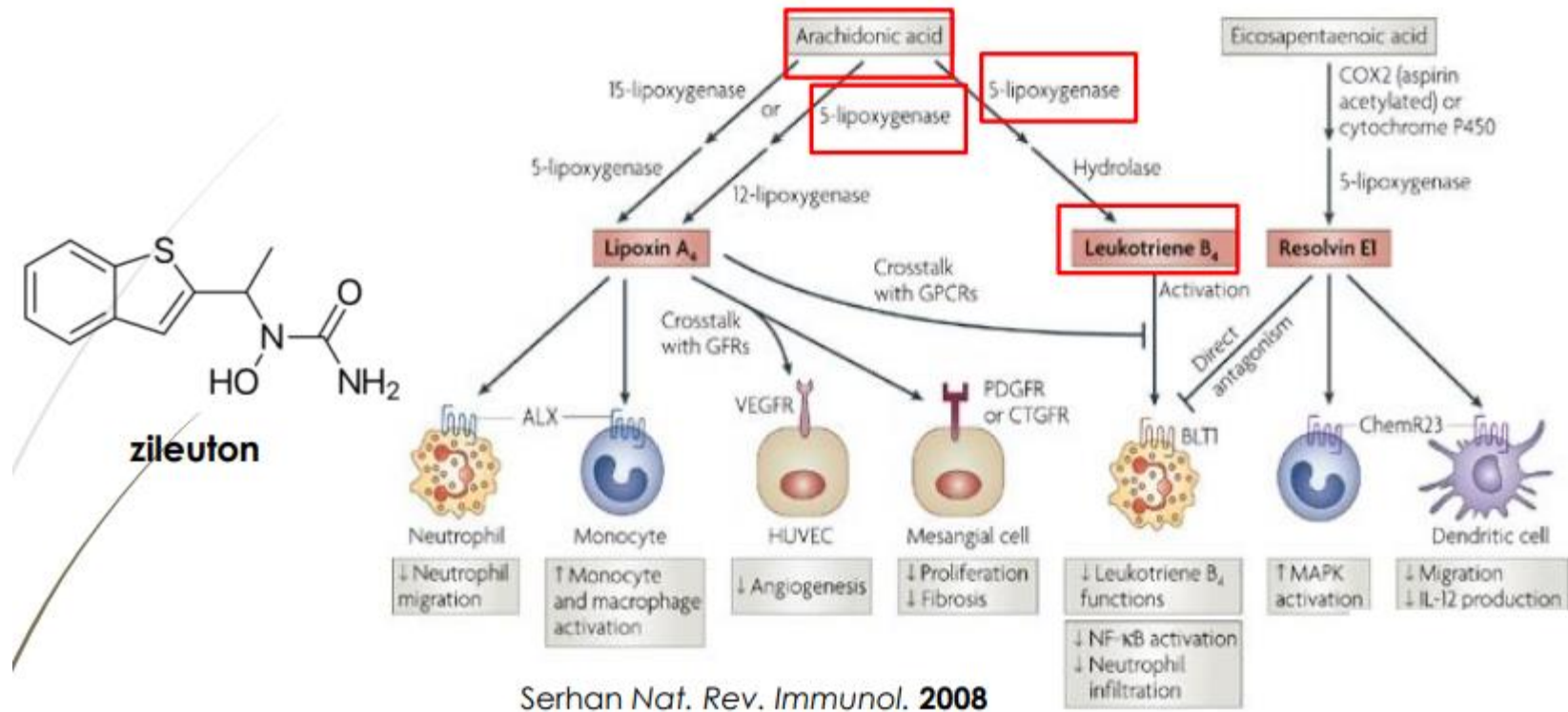


NEW TREATMENT TO PREVENT ASTHMA

December 4th 2024, Biocitech Paris-Romainville

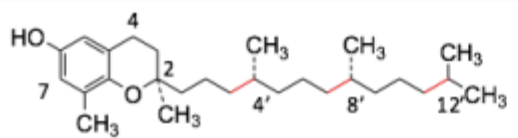
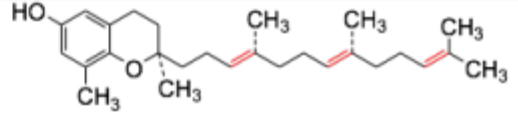
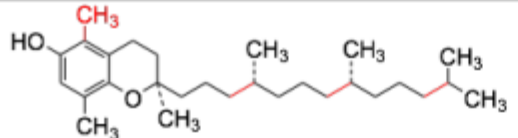
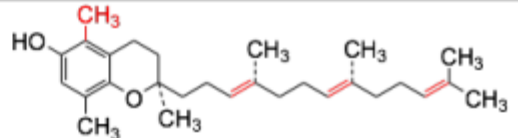
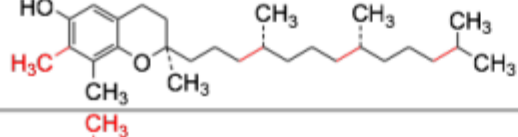
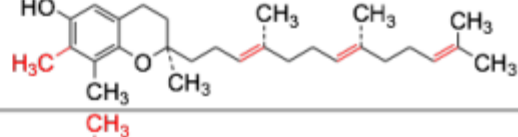
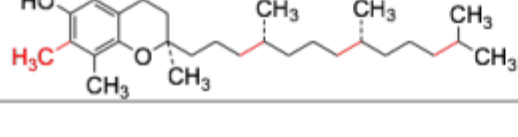
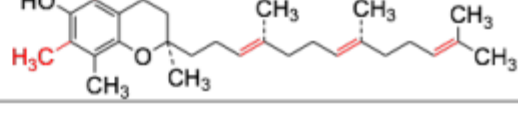


5-lipoxygenase (5-LO) pathway



- ✓ **5-LO pathway : Arachidonic acid (AA) => potent proinflammatory leukotrienes (LTs)**
- ✓ **Asthma, atopic dermatitis, cardiovascular diseases, cancers...**

Vitamin E isoforms : 4 tocopherols + 4 tocotrienols

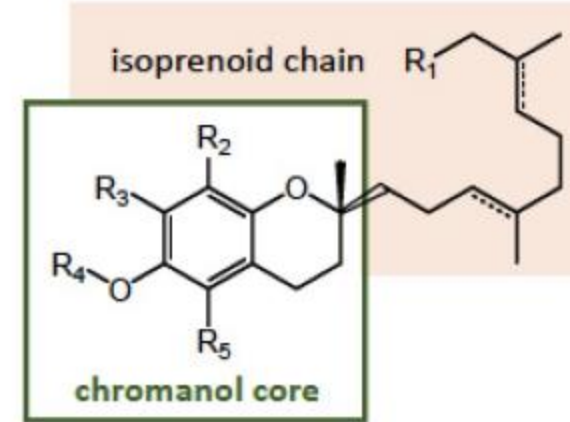
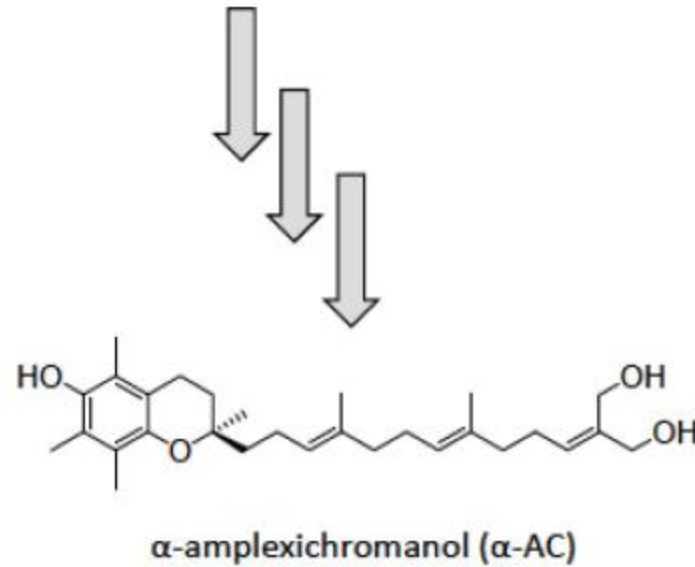
	Tocopherols : T	Tocotrienols : TE or T3	
δ-tocopherol (δ-T)		δ-tocotrienol (δ-T3)	
β-tocopherol (β-T)		β-tocotrienol (β-T3)	
γ-tocopherol (γ-T)		γ-tocotrienol (γ-T3)	
α-tocopherol (α-T)		α-tocotrienol (α-T3)	

Pharmacomodulation : > 90 TE Derivatives

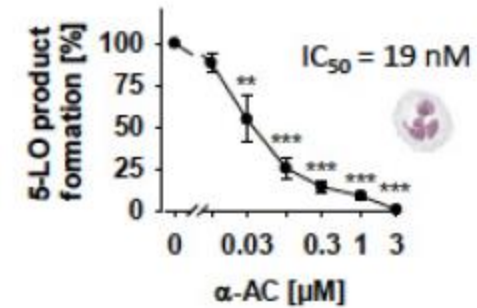
Development of LCM-derived 5-lipoxygenase inhibitors

Library of vitamin E derivatives
















- 8 natural vitamin E forms
- 16 potential endogenous metabolites
- 73 plant-derived or semi-synthetic derivatives



5-LO activity in PMNL (A23187/AA)

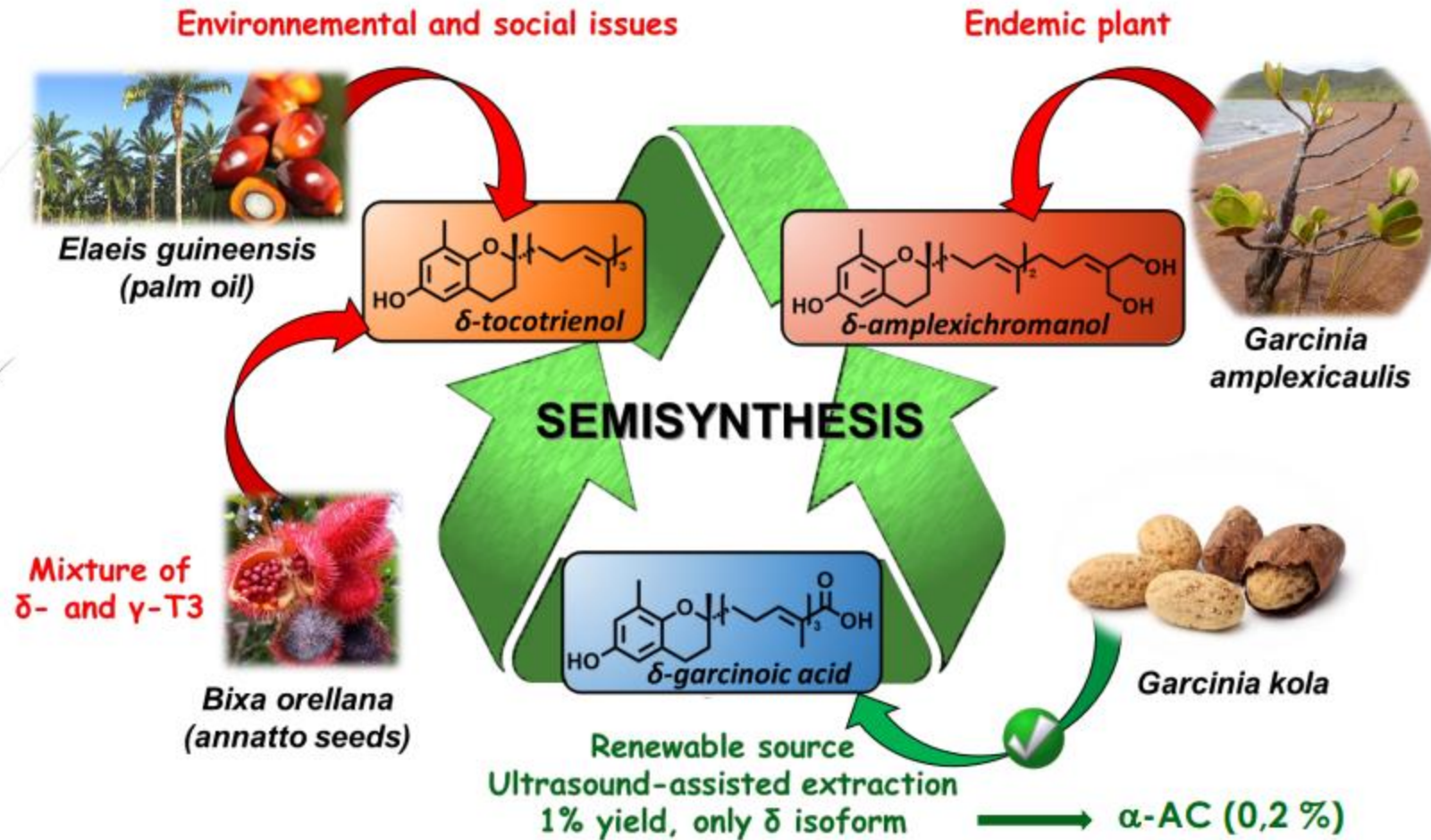


Best candidate : α -AC : Pharmacological profile

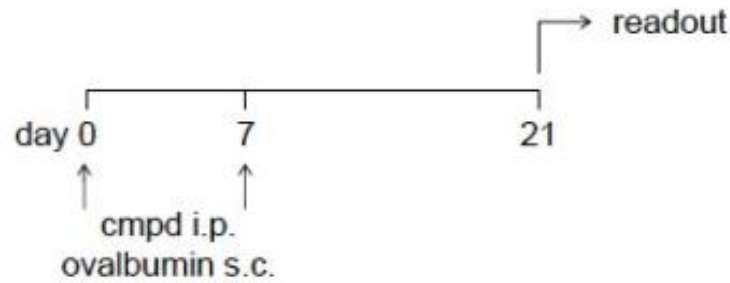
assay	IC ₅₀ /EC ₅₀ [μ M]	
 5-LO enzyme	0.106	5-LO
 5-LO in PMNL (A23187/AA)	0.019	
 5-LO in monocytes	0.898	
 radical scavenging	7.696	others
 Ca ²⁺ -influx	> 10	
 12-LO in PMNL	> 3	
 15-LO in PMNL	> 3	
 COX-1 enzyme	> 10	
 COX-1 in platelets	> 10	
 COX-2 enzyme	> 10	
 mPGES-1 in microsomes	> 10	
 LTC ₄ synthase	> 10	
 Viability of PBMC (24 h)	n.i. at 10	
 Viability of differentiated HepaRG cells (48 h)	n.i. at 10	
 CYP3A4 induction in differentiated HepaRG cells	> 10	drug interference

Zileuton : 0.4

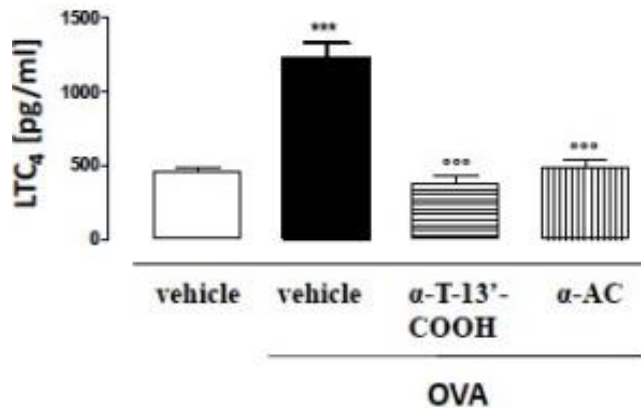
α -AC : Semisynthesis



Preclinical studies : α -AC reduces bronchial hyper-reactivity in murine asthma

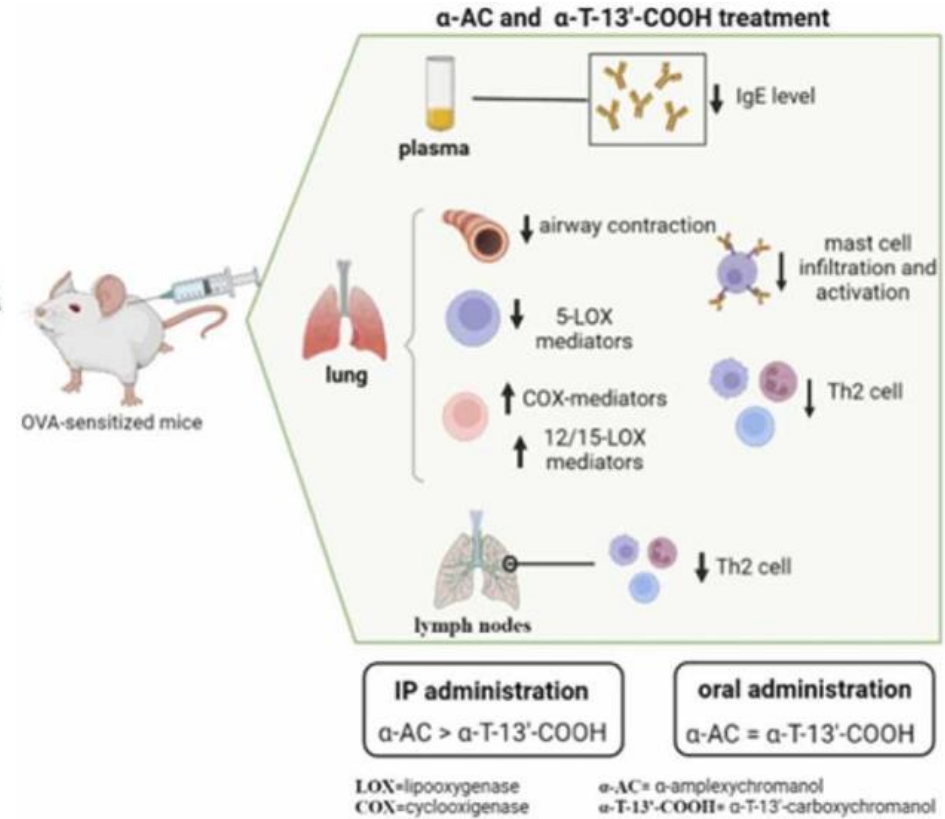
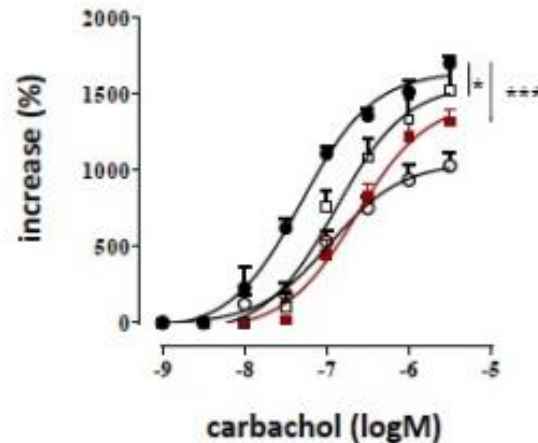


pulmonary cysteinyl leukotrienes



bronchial hyper-reactivity

- vehicle
- vehicle + OVA
- α -T-13'-COOH + OVA
- α -AC + OVA



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A vitamin E long-chain metabolite and the inspired drug candidate α -amplexichromanol relieve asthma features in an experimental model of allergen sensitization

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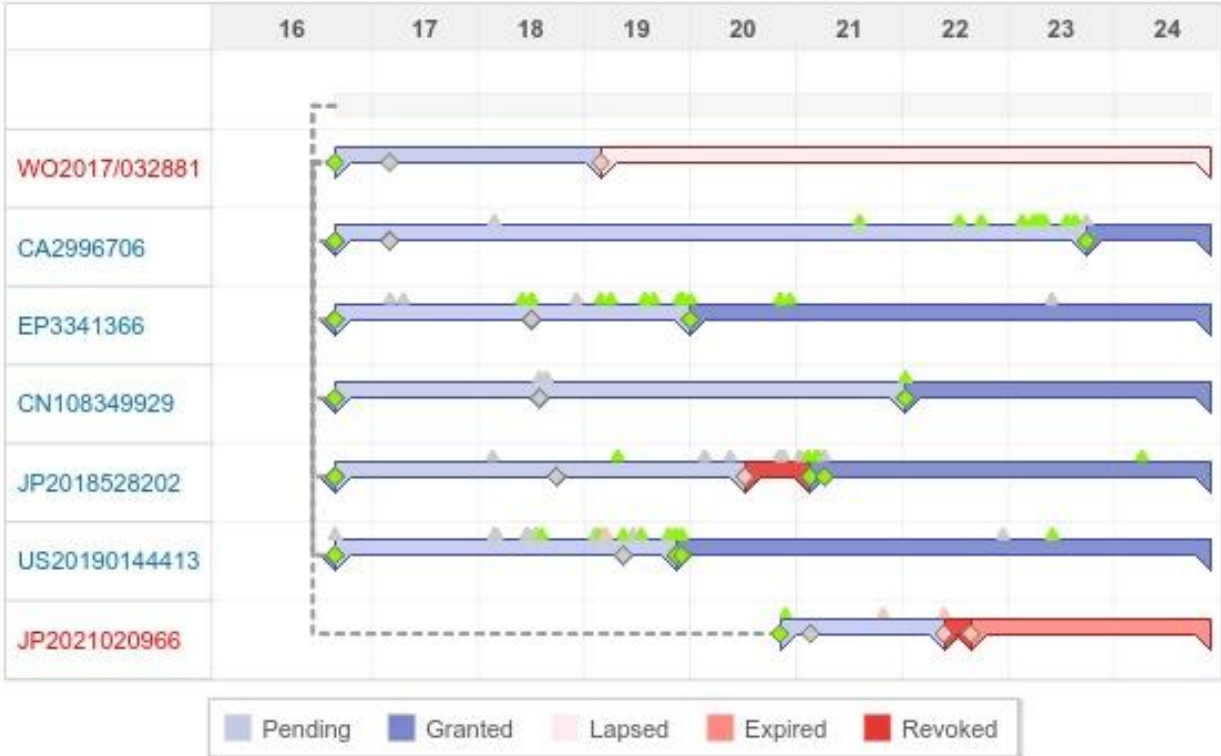
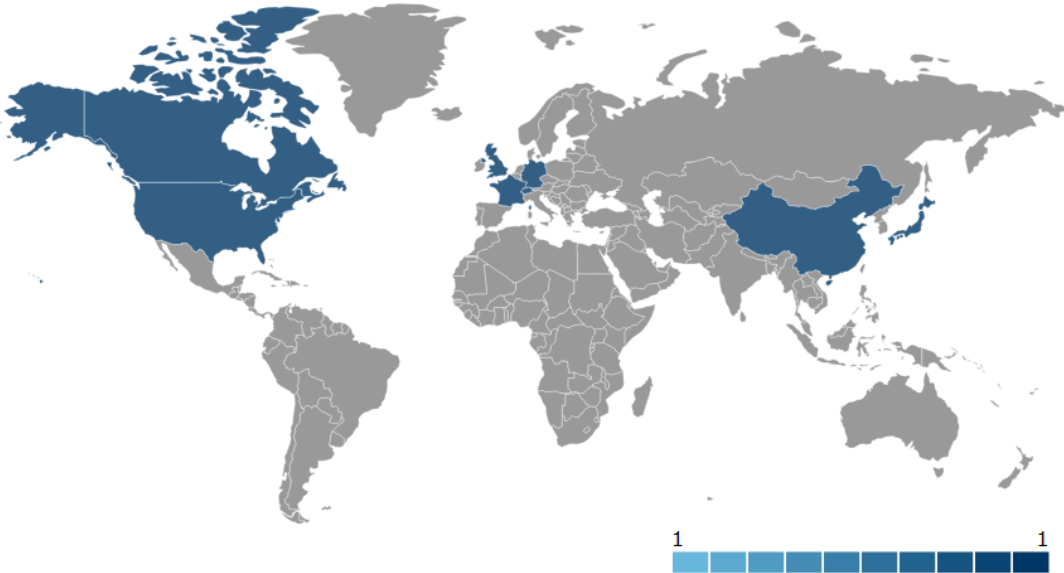
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