NOUVELLES CIBLES THERAPEUTIQUES DANS LES MALADIES AUTOINFLAMMATOIRES

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Centre de référence des amyloses d'origine inflammatoire et de la fièvre méditerranéenne familiale, Hôpital Tenon, Paris

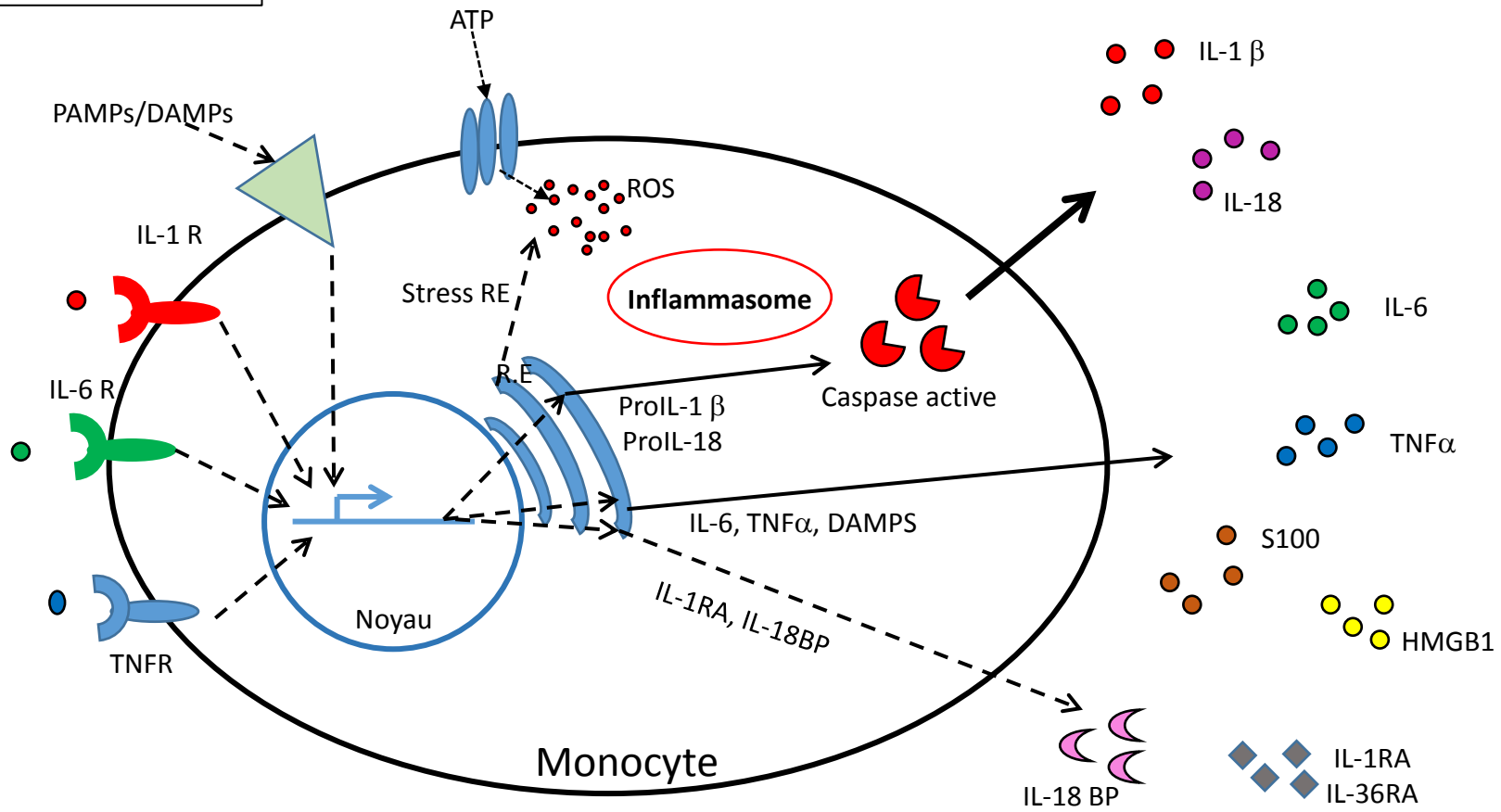
Colloque du CEREMAI, Montpellier, le Vendredi 16 Octobre 2015

PLAN

- Traitement en fonction du mécanisme physiopathologique
- => nouvelles thérapies ciblées
- Approche par type cellulaire
- Déficit immunitaire et MAI
- Amylose AA

STRESS DU RETICULUM ENDOPLASMIQUE:
Défaut de repliement des protéines ou défaut de modifications post translationnelles: augmentation du stress RE =>Secretion accrue de ROS => production Il1β

INFLAMMASOMOPATHIES: mutations gain de fonction des inflammasommes: secretion d'Il1β et IL18

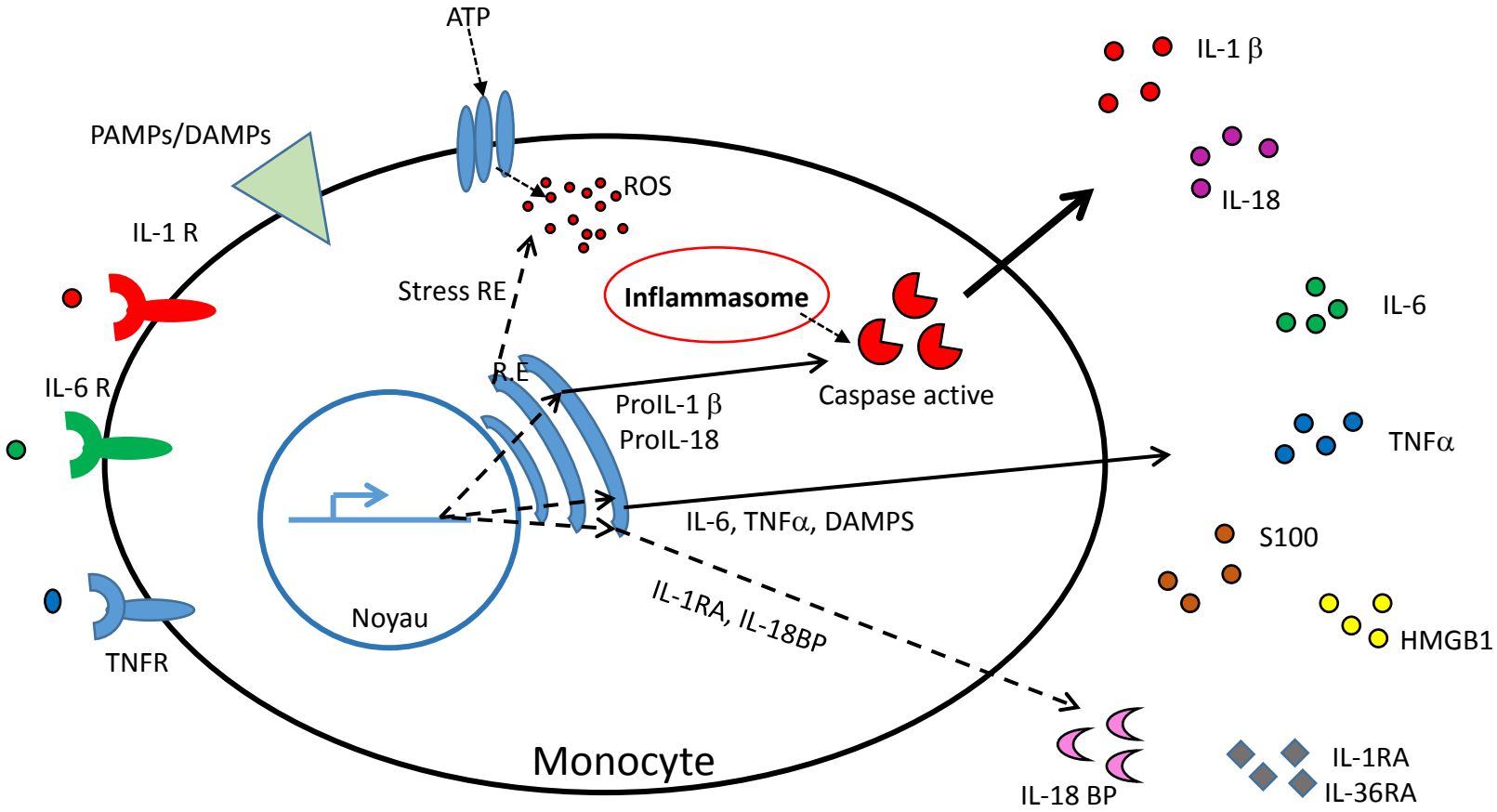


INTERFERONOPATHIES: augmentation de l'expression du gene de l'INF et de l'inflammation

Déséquilibre des antagonistes endogènes: Mutations *IL1RN, IL36RN*

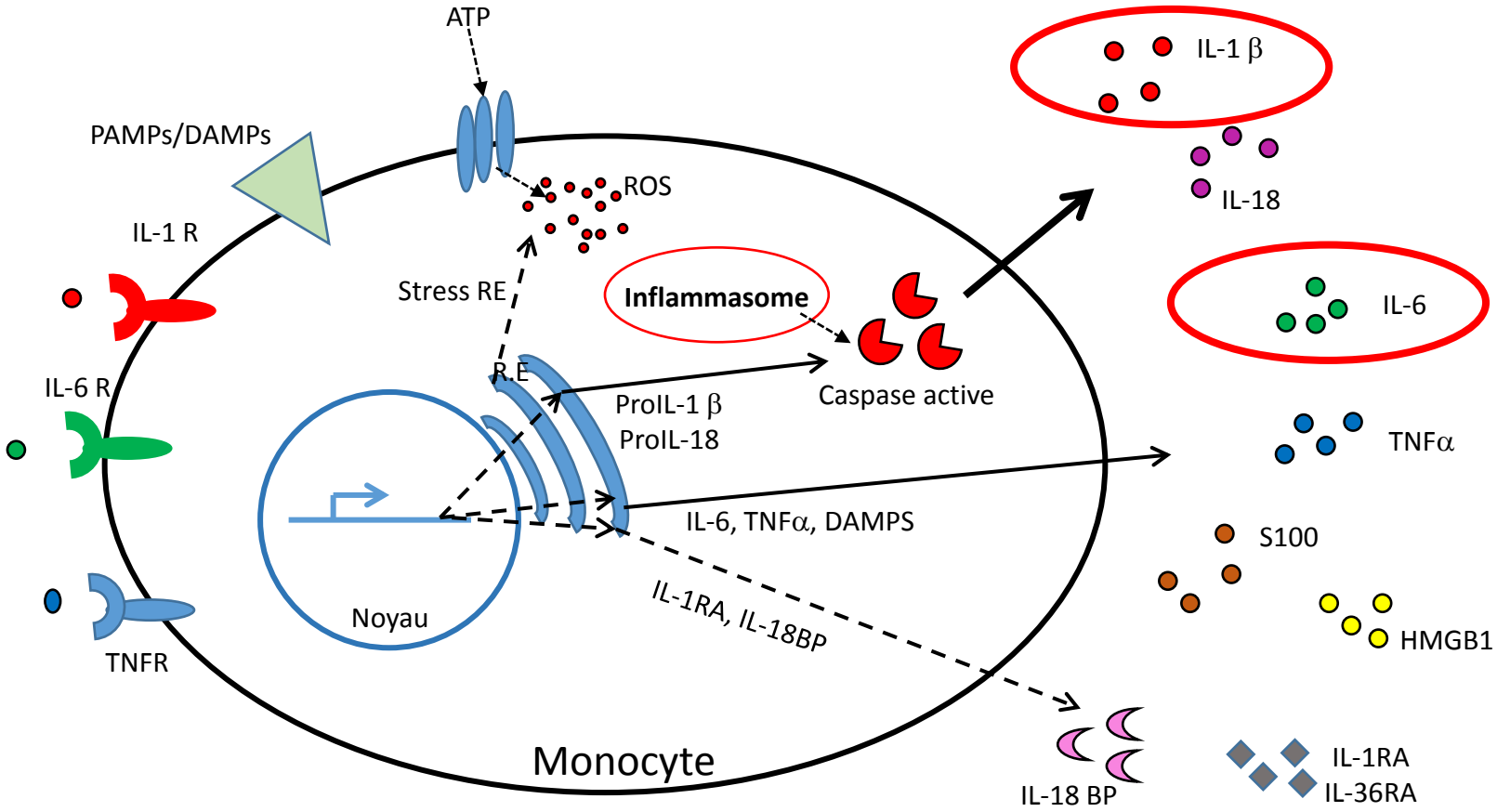
Adapted from Holzinger, Nat Rev Rheum, 2015

INFLAMMASOMOPATHIES: mutations gain de function des inflammasommes: secretion d'Il1β et IL18



Holzinger, Nat Rev Rheum, 2015

INFLAMMASOMOPATHIES: mutations gain de function des inflammasommes: secretion d'Il1β et IL18



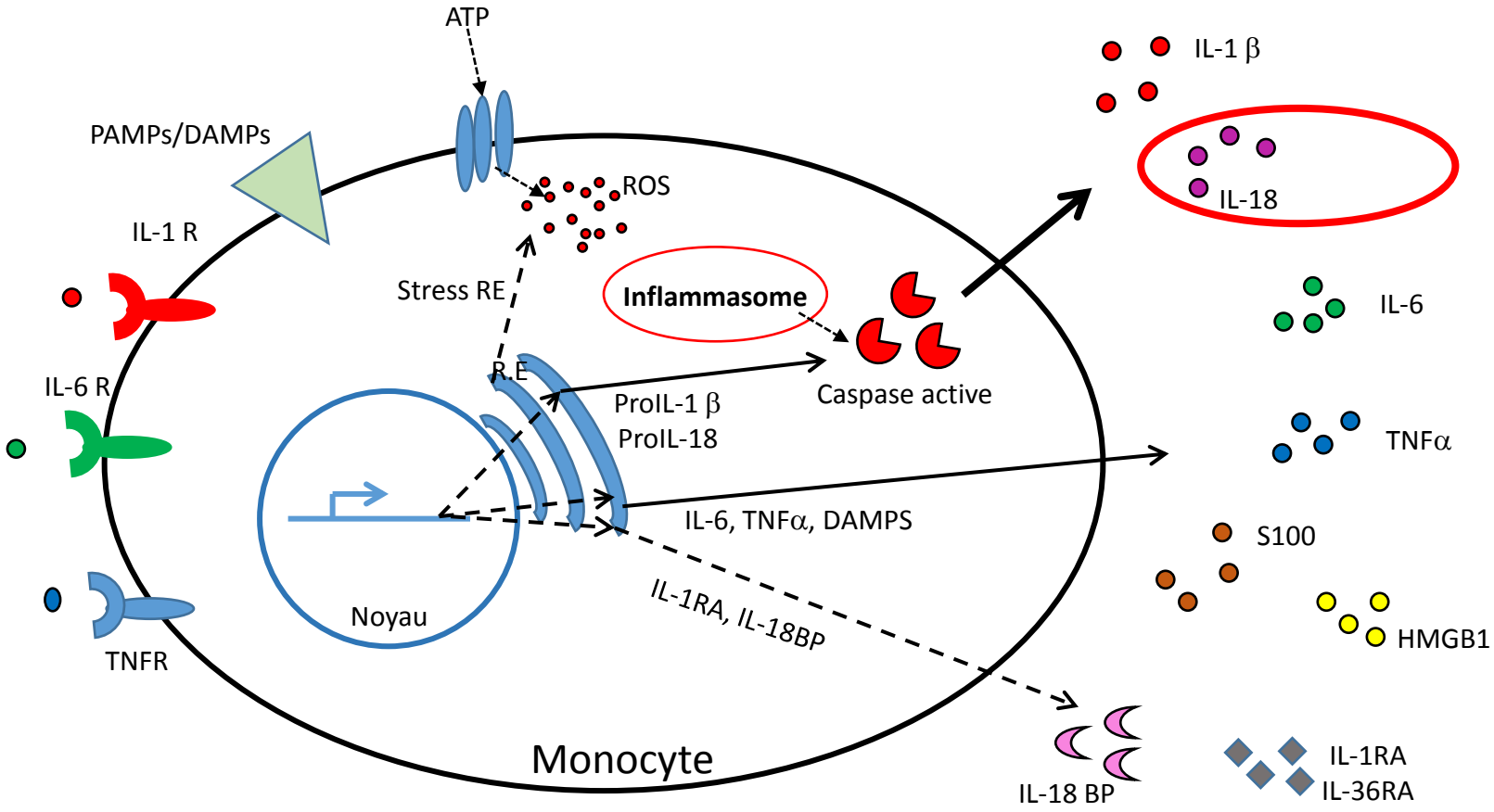
Holzinger, Nat Rev Rheum, 2015

Utilisation élargie de biothérapies connues (ISSAID 2015)

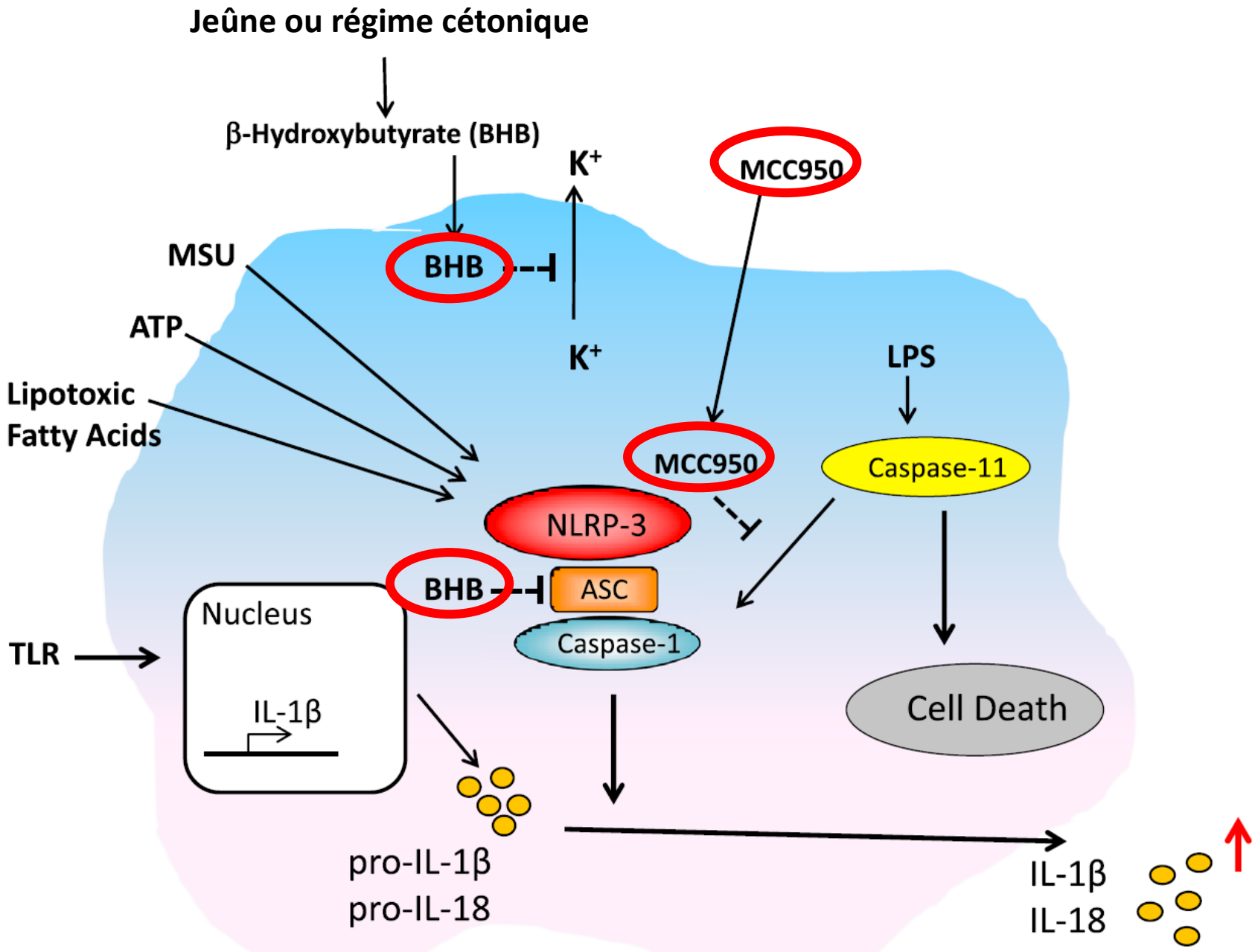
- **Bloqueurs de l'IL1:**
  - **TRAPS (au long cours ou à la demande)**
  - **HIDS**
  - **FMF résistant à la colchicine**
  - **Schnitzler**
  - **MAI inclassées**
  - **Amylose AA d'origine inconnue**

- **Bloqueurs de l'IL6:**
  - **Amylose AA d'origine inconnue ou associée à un rhumatisme inflammatoire**

BIOTHERAPIE FUTURE: anti IL18

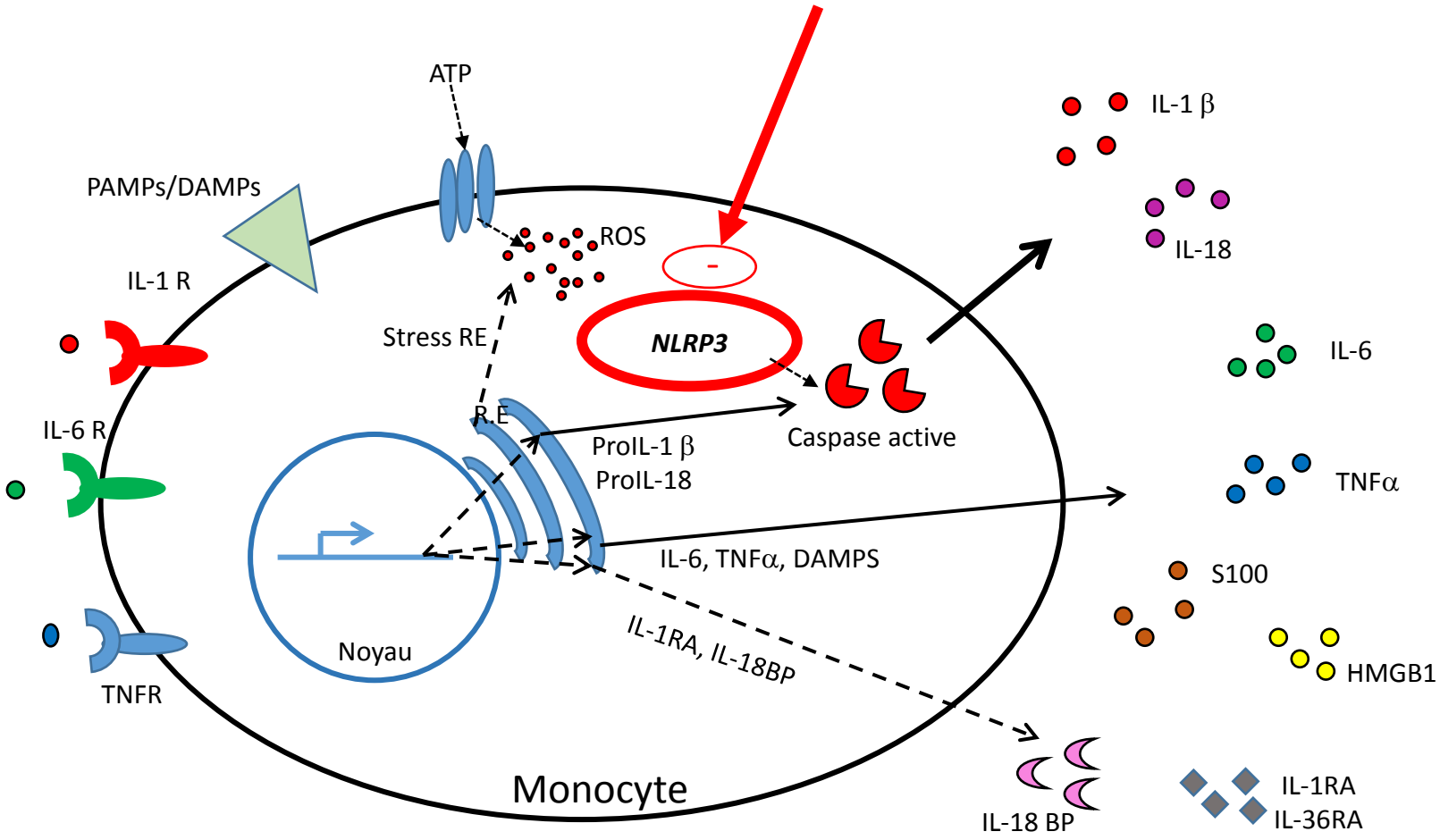


Holzinger, Nat Rev Rheum, 2015



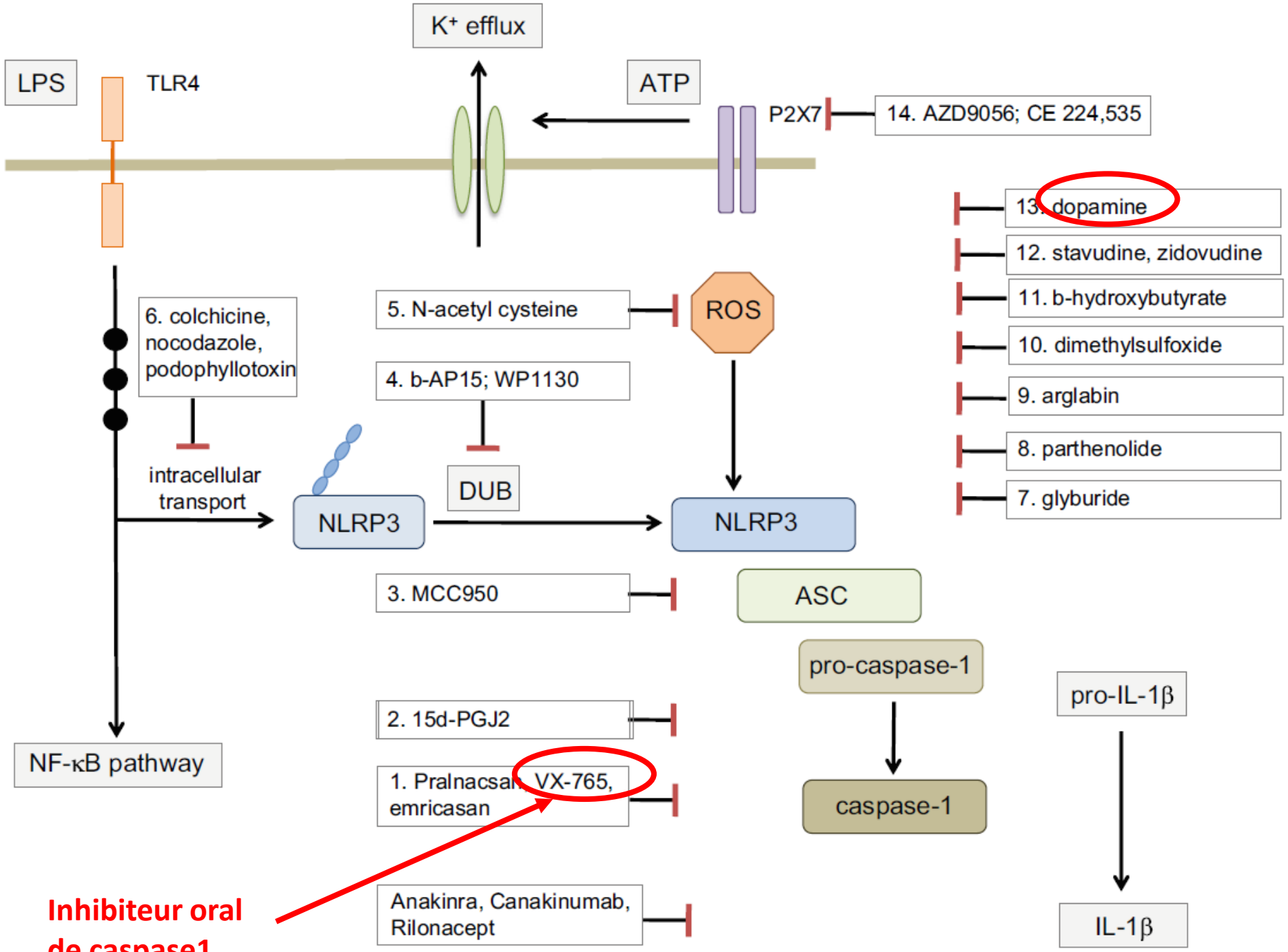
Coll, Nat Med 2015, Youm Nat Med 2015, Netea Cell Metab 2015

INHIBITEURS DE *NLRP3*



Rôle du régime cétogénique?

Coll, Nat Med 2015, Youm Nat Med 2015, Netea Cell Metab 2015



Intérêt ? d'agonistes du R1 à la dopamine

Inhibiteur oral de caspase1

Kallinich, 2015 Semin Immunopath

DÉFICIT EN MÉVALONATE KINASE

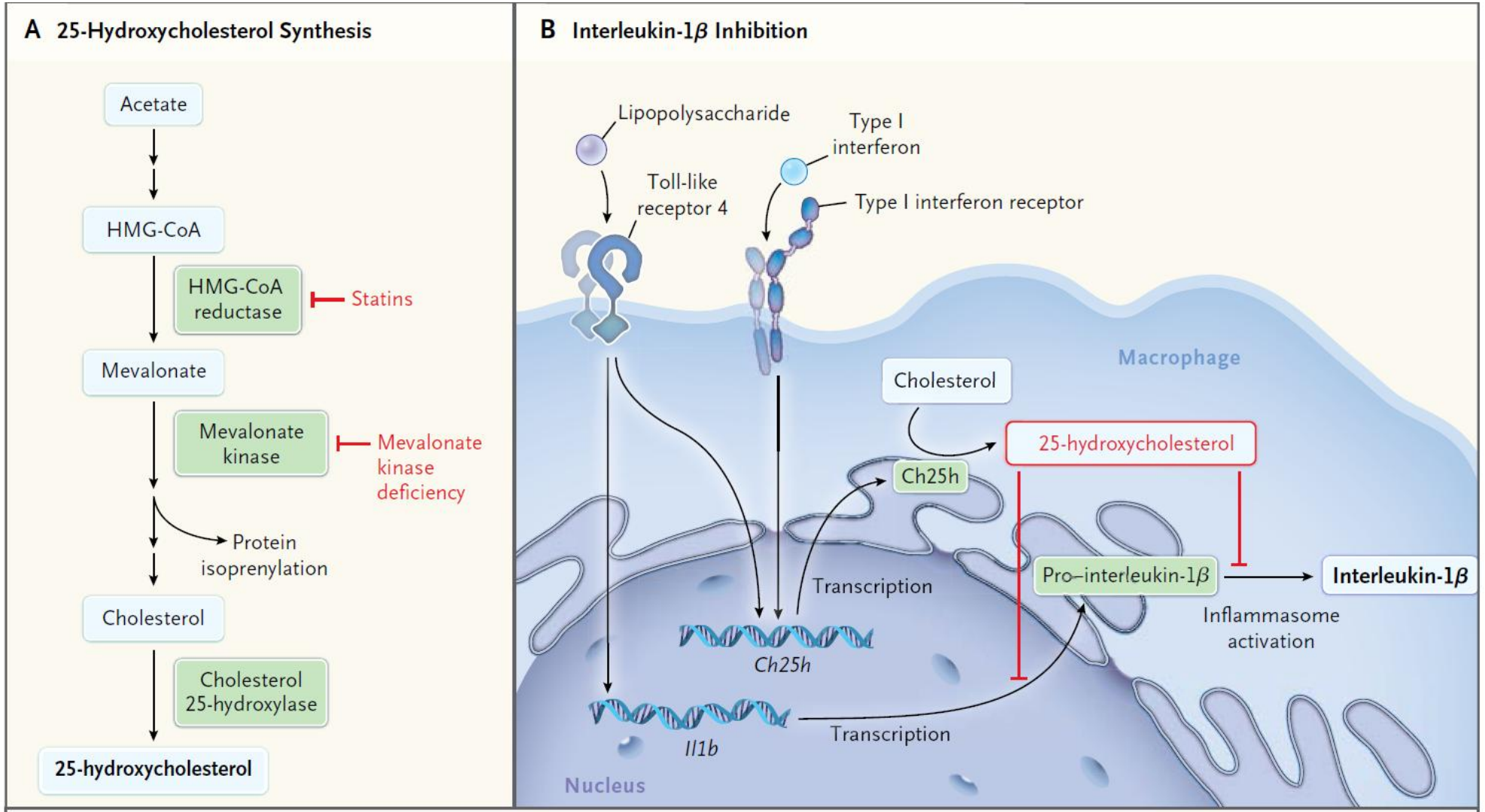
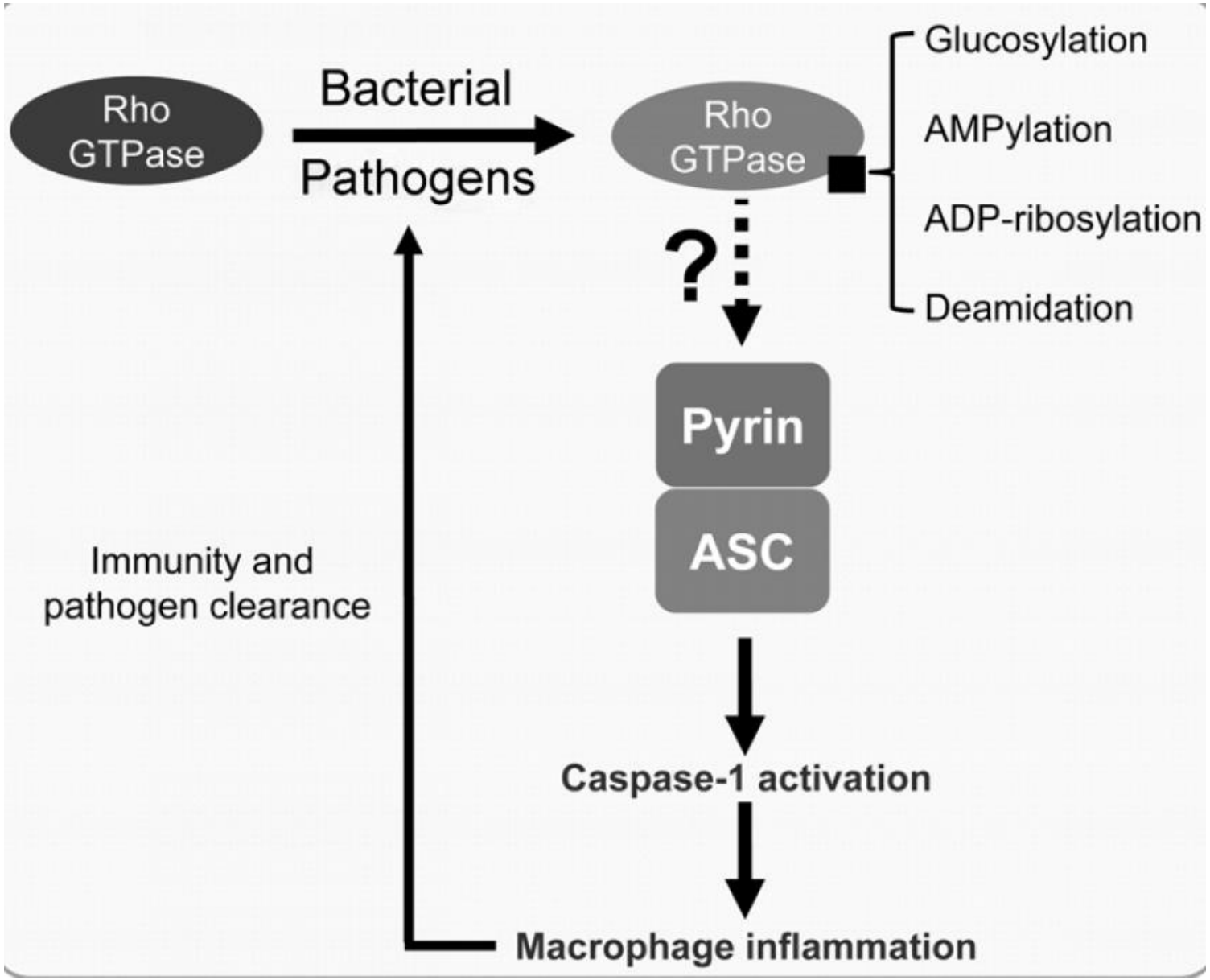


Figure 1. Derivation of 25-Hydroxycholesterol and the Inhibition of Interleukin-1β by 25-Hydroxycholesterol.

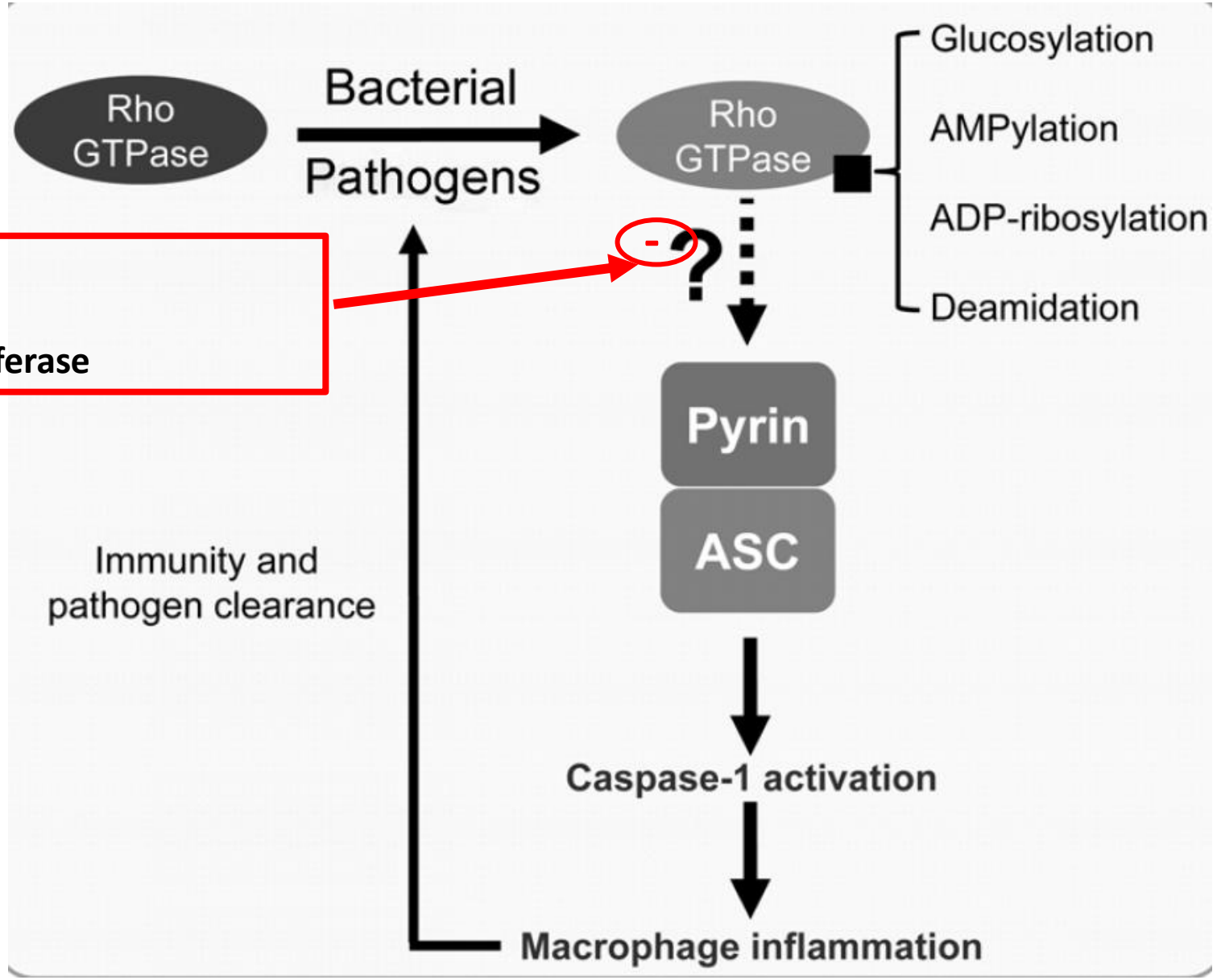
Simon, 2014, NEJM



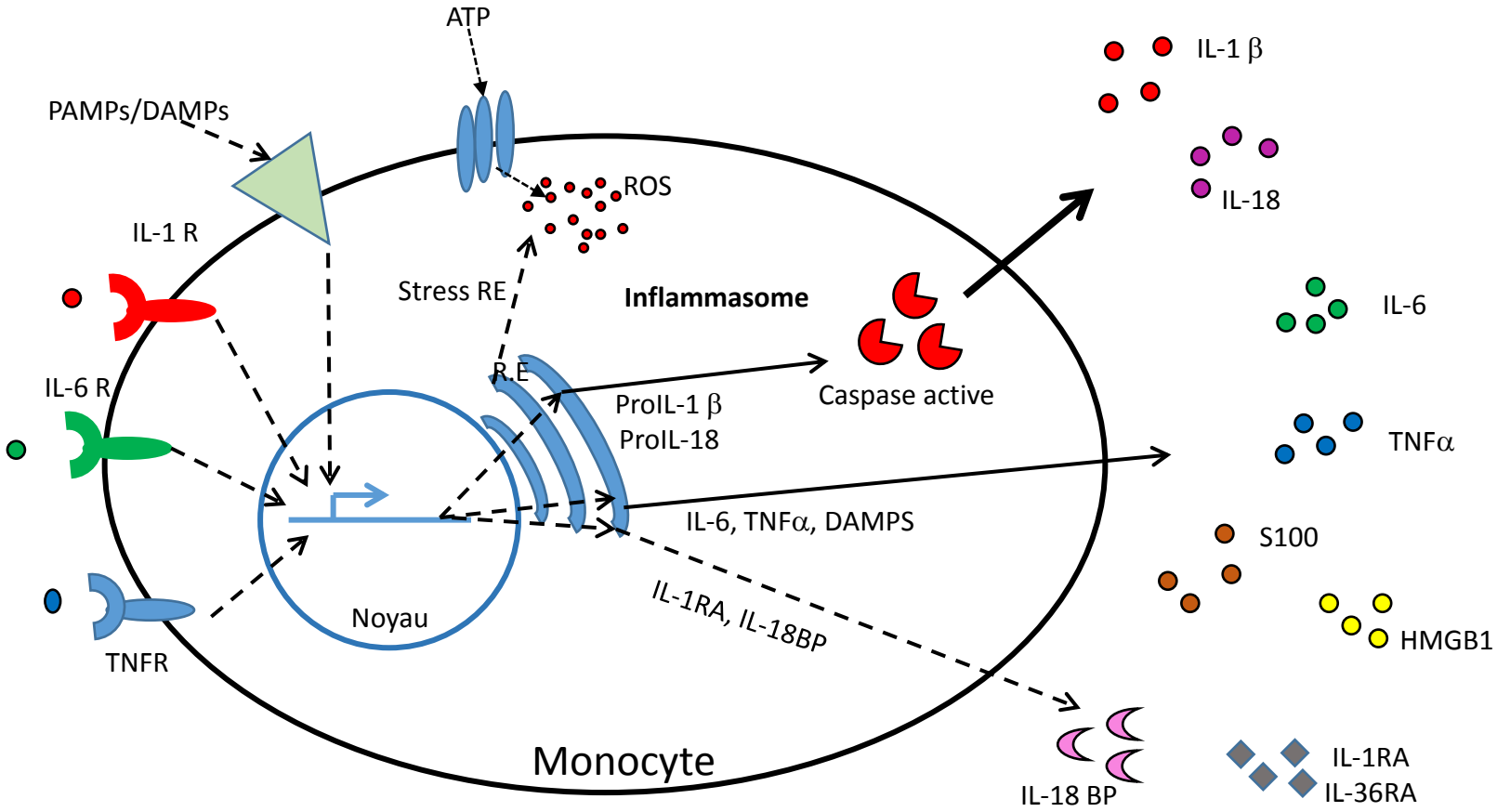
Yang, 2014, Sci, Cin Lif Sci; Xu, Nature, 2014

Déficit en mévalonate kinase

Inhibiteurs de la voie du mévalonate:
-inhibiteurs de la farnesyl transferase
-inhibiteurs de la geranylgeranyltransferase



Yang, 2014, Sci, Cin Lif Sci; Xu, Nature, 2014



INTERFERONOPATHIES: augmentation de l'expression du gene de l'INF et de l'inflammation

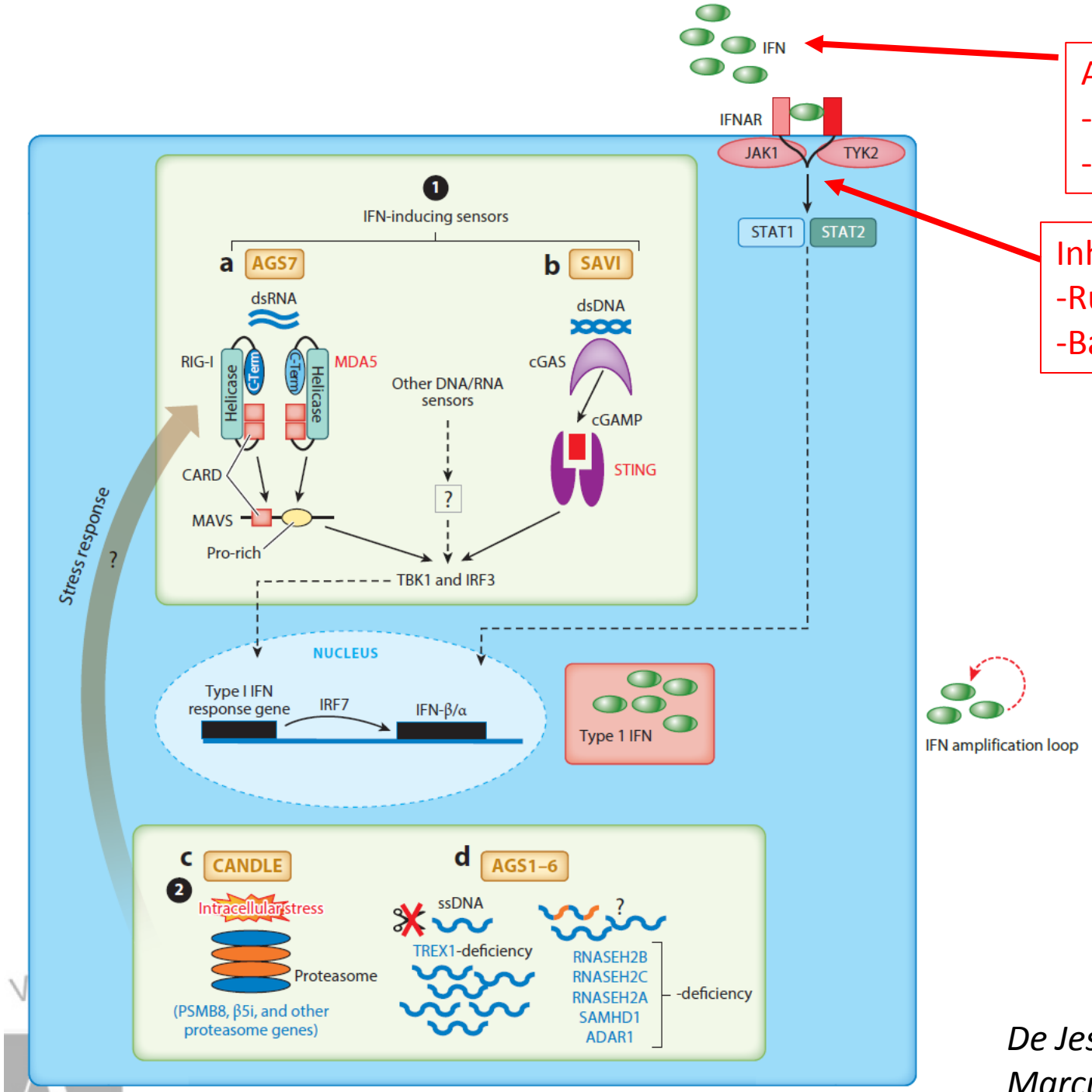
Adapted from Holzinger, Nat Rev Rheum, 2015

Interféronopathies type 1

-SAVI

-Sd Aicardi-Goutières

-Mutations du protéasome



Anti INF :
-Sifalimumab
-Rontalizumab

Inhibiteurs de JAK2:
-Ruxolitinib
-Baricitinib

IFN amplification loop

De Jesu, 2015, Ann Rev Immunol
Marcuzzi, Int J Mol Sci 2015

Efficacy of JAK 1/2 inhibition in two children with inherited STING-activating mutation

ML. Frémond[1], D. Bessis[2], E. Jeziorski[3], J. Munoz[2], N. Jeremiah[4,5], A. Hulin[6], F. Rieux-Laucat[4,5], C. Bodemer[7], B. Bader-Meunier[1,4,5], YJ. Crow[4,8], S. Blanche[1] B. Neven[1,4,5]

[1]Pediatric Hematology-Immunology and Rhumatology Department, Hôpital Necker, AP-HP, Paris, France, [2]Dermatology Department and [3]Pediatrics department, Centre Hospitalier Universitaire de Montpellier, Montpellier, France, [4]Institut Imagine, Paris, France, [5]INSERM UMR 1163, Laboratory of Immunogenetics of Pediatric Autoimmunity, Paris, France, [6]Pharmacology and Toxicology Department, Hôpital Universitaire Henri Mondor, Créteil, France, [7]Dermatology Department, Hôpital Necker, AP-HP, Paris, France, [8]INSERM UMR 1163, Laboratory of Neurogenetics and Neuroinflammation, Paris, France.

INTRODUCTION

Activating mutations of the *TMEM173* encoding STING (stimulator of interferon genes) have been recently described and underlie a new interferonopathy. STING is a key molecule in the cytosolic DNA-sensing pathway that leads to transcription of type-I interferon (IFN) genes. The Janus kinases (JAK) are activated upon IFN receptor stimulation, which then leads to release of IFN stimulated genes. We report on two children with *STING*-activating mutation treated with ruxolitinib, a JAK1-2 inhibitor.

PATIENTS and METHODS

Patient 1 (P1), a 4-year-old girl, presented with recurrent fever, failure to thrive and tachypnoea from a few months of age. She exhibited markers of chronic systemic inflammation (CRP - 50 to 100 mg/l; chronic anaemia - 8 to 10 g/dl) and a sustained type-I IFN signature. Chest-CT scan demonstrated interstitial lung disease and fibrosis (figure 1a).

Patient 2 (P2), a 6-year-old boy, presented from the age of 2 months with severe skin vasculitis of feet, hands (figure 2a), nose and cheeks, failure to thrive and mild lung disease. No elevation of inflammatory markers was present.

Both patients were previously treated with steroids, anti-CD20 monoclonal antibodies and mycophenolate mofetil without obvious therapeutic efficacy. Both patients carry a germline dominant gain-of-function mutation in *STING*.

Ruxolitinib was introduced at the initial dose of 2.5 mg twice daily (for a body weight of 10.5 and 16 kg respectively). Follow-up is 12 months in P1 and 3 months in P2.

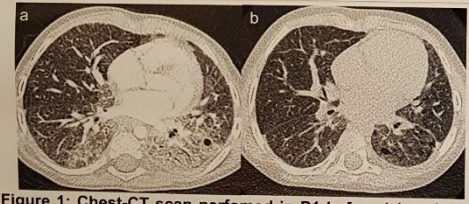


Figure 1: Chest-CT scan perfomed in P1 before (a) and one year after (b) introduction of ruxolitinib.

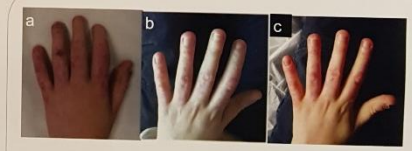


Figure 2: Pictures of the hands vasculitis of P2 before (a) and after one (b) and three (c) months of ruxolitinib.

RESULTS

P1: Significant improvement of general condition was noticed with gain of 0.5 SD of weight and reduced frequency of fevers. Tachypnoea normalised, and lung fibrosis apparently improved (figure 1b). CRP ranged from 8 to 25 mg/l, and haemoglobin stable at around 11 g/dl. Steroids were tapered from 1 mg/kg to 0.2 mg/kg/d. P2: improvement of the vasculitis (figure 2b and 2c) and general condition was noticed. There was a reduction in the interferon score in both cases.

Tolerance of ruxolitinib was good, allowing for an increase in dosage in P2 to 5 mg twice daily. P1 presented with papillary oedema related to idiopathic intracranial hypertension during treatment, a side effect not reported previously.

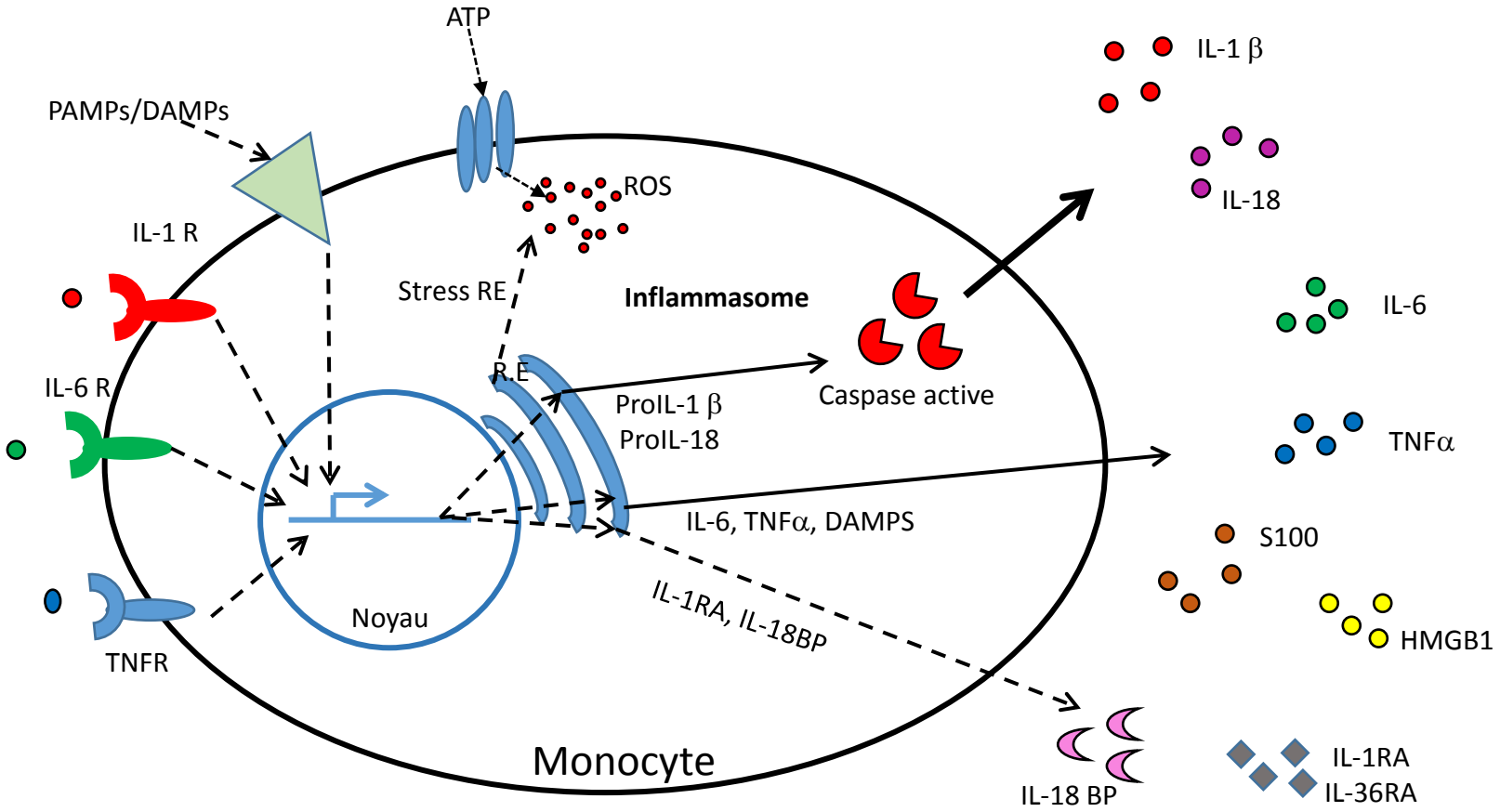
CONCLUSION

We report the first use of ruxolitinib in two patients with *STING*-activating mutation, suggesting improvement of inflammatory related symptoms and skin lesions. These promising results need to be confirmed, and possible benefits on lung fibrosis needs to be evaluated.

Fremond, Poster ISSAID 2015

STRESS DU RETICULUM ENDOPLASMIQUE:

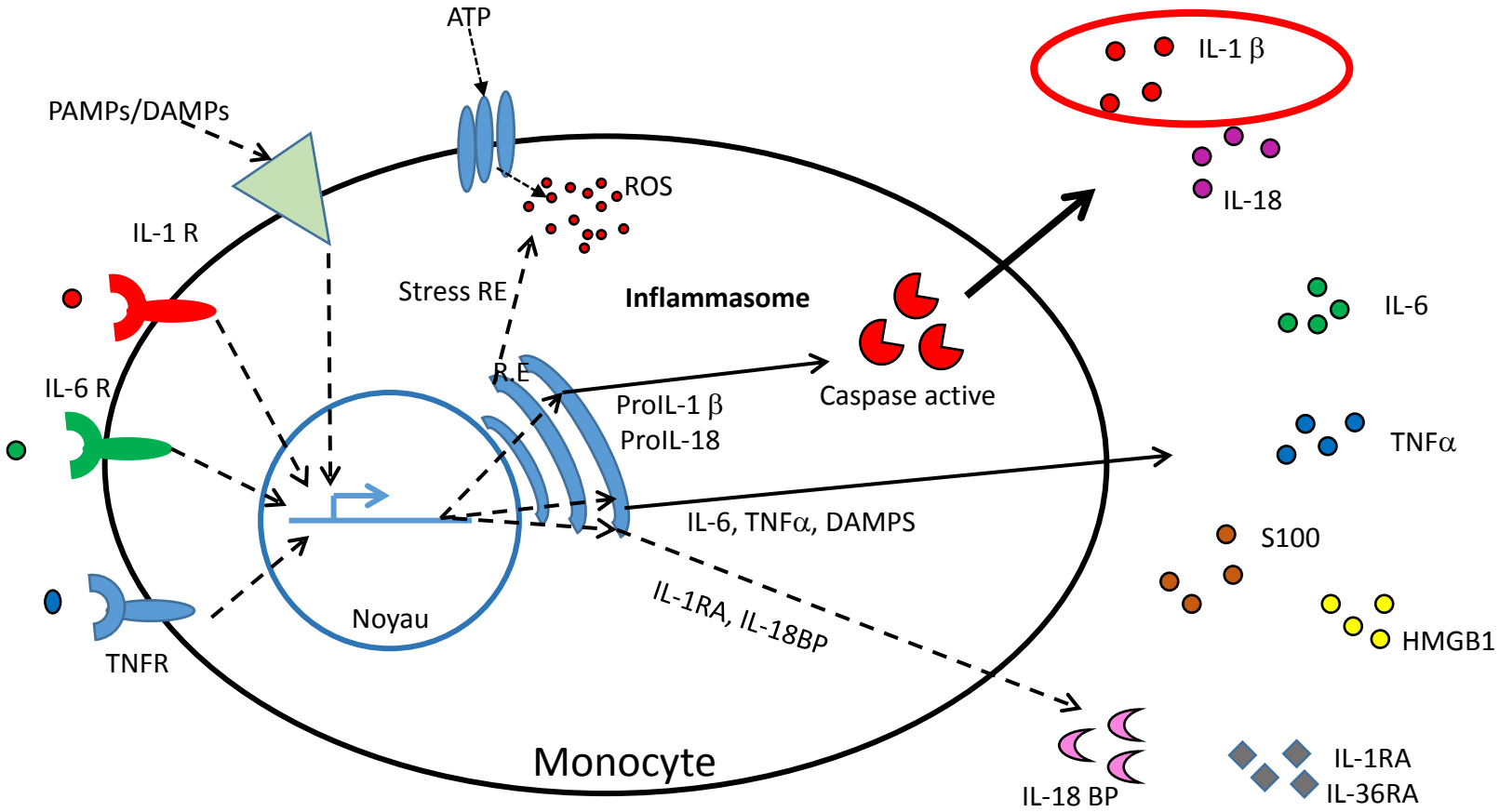
Défaut de repliement des protéines ou défaut de modifications post translationnelles: augmentation du stress RE =>Secretion accrue de ROS => production Il1β



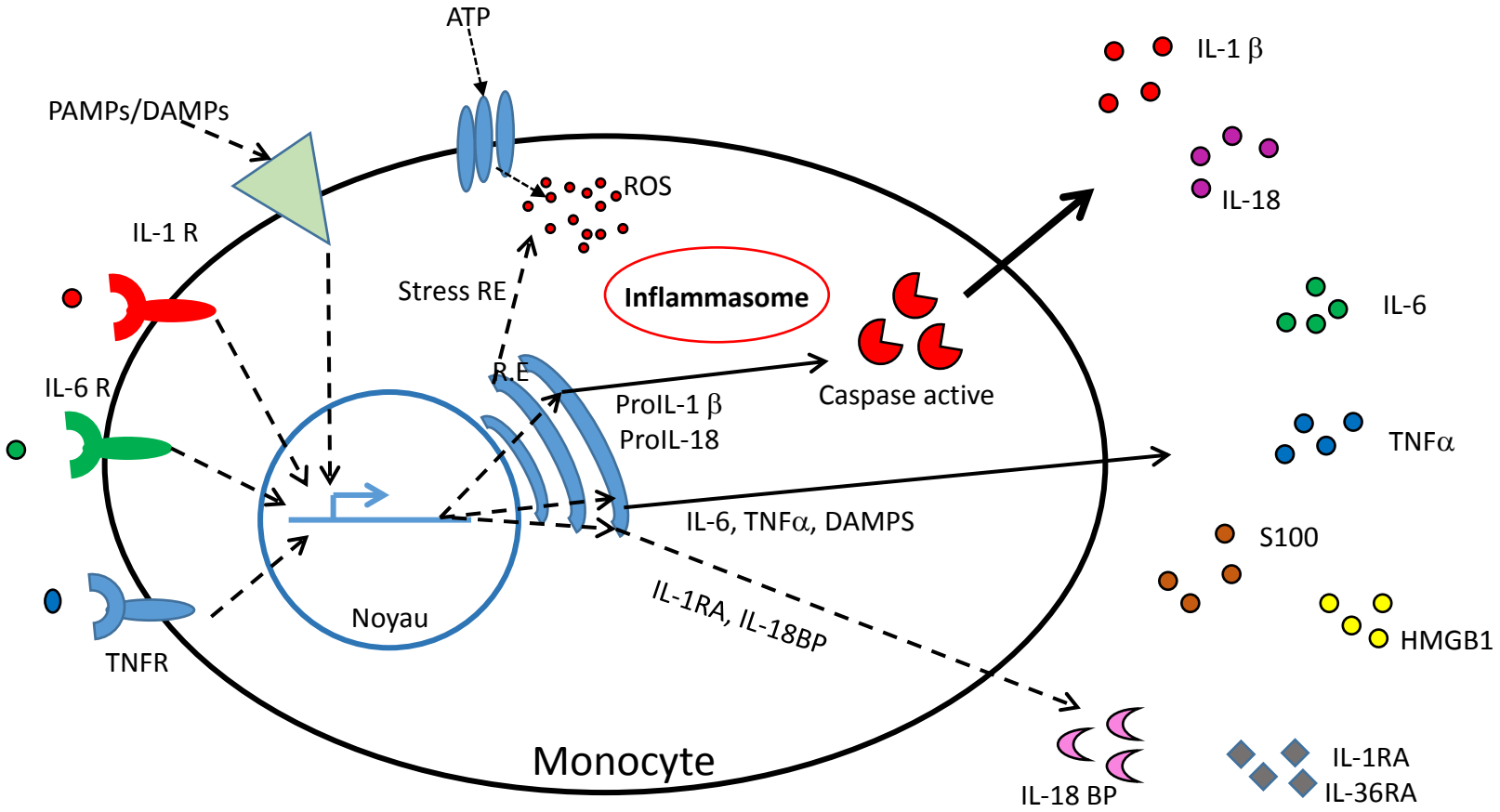
Adapted from Holzinger, Nat Rev Rheum, 2015

STRESS DU RETICULUM ENDOPLASMIQUE:
Défaut de repliement des protéines ou défaut de modifications post translationnelles: augmentation du stress RE =>Secretion accrue de ROS => production Il1β

Anti IL1 dans TRAPS

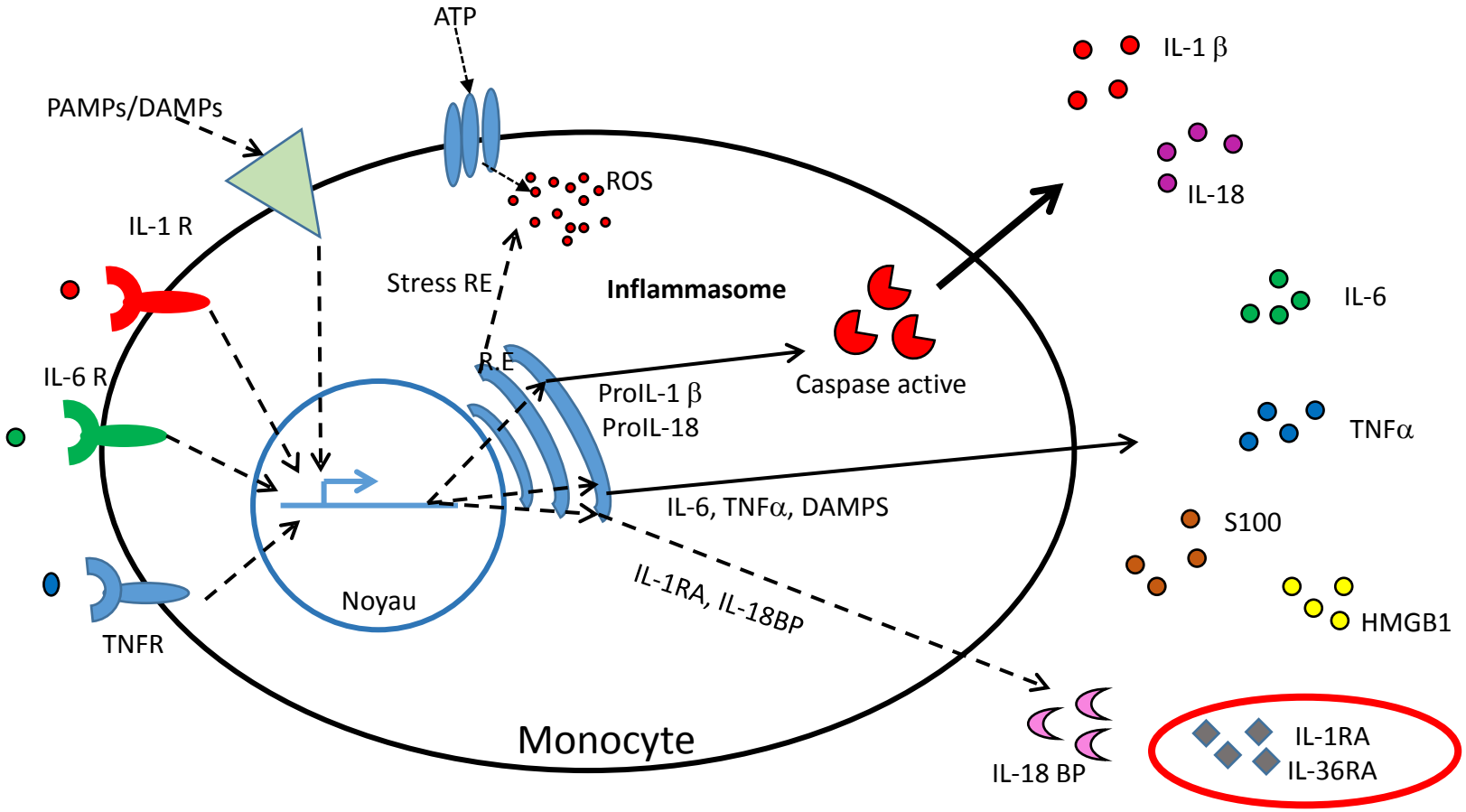


Adapted from Holzinger, Nat Rev Rheum, 2015



Déséquilibre des antagonistes endogènes:
Mutations *IL1RN, IL36RN*

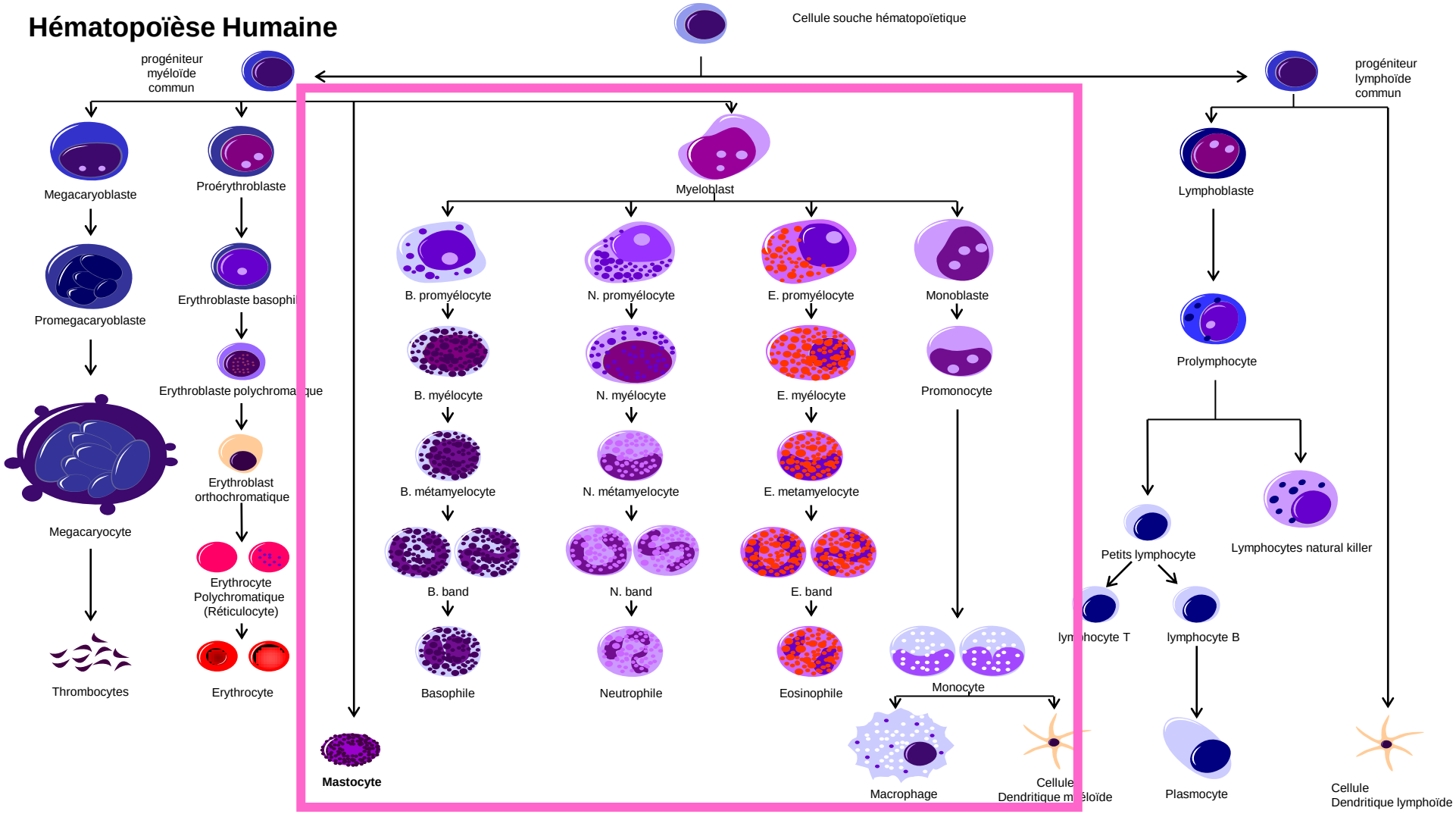
Adapted from Holzinger, Nat Rev Rheum, 2015

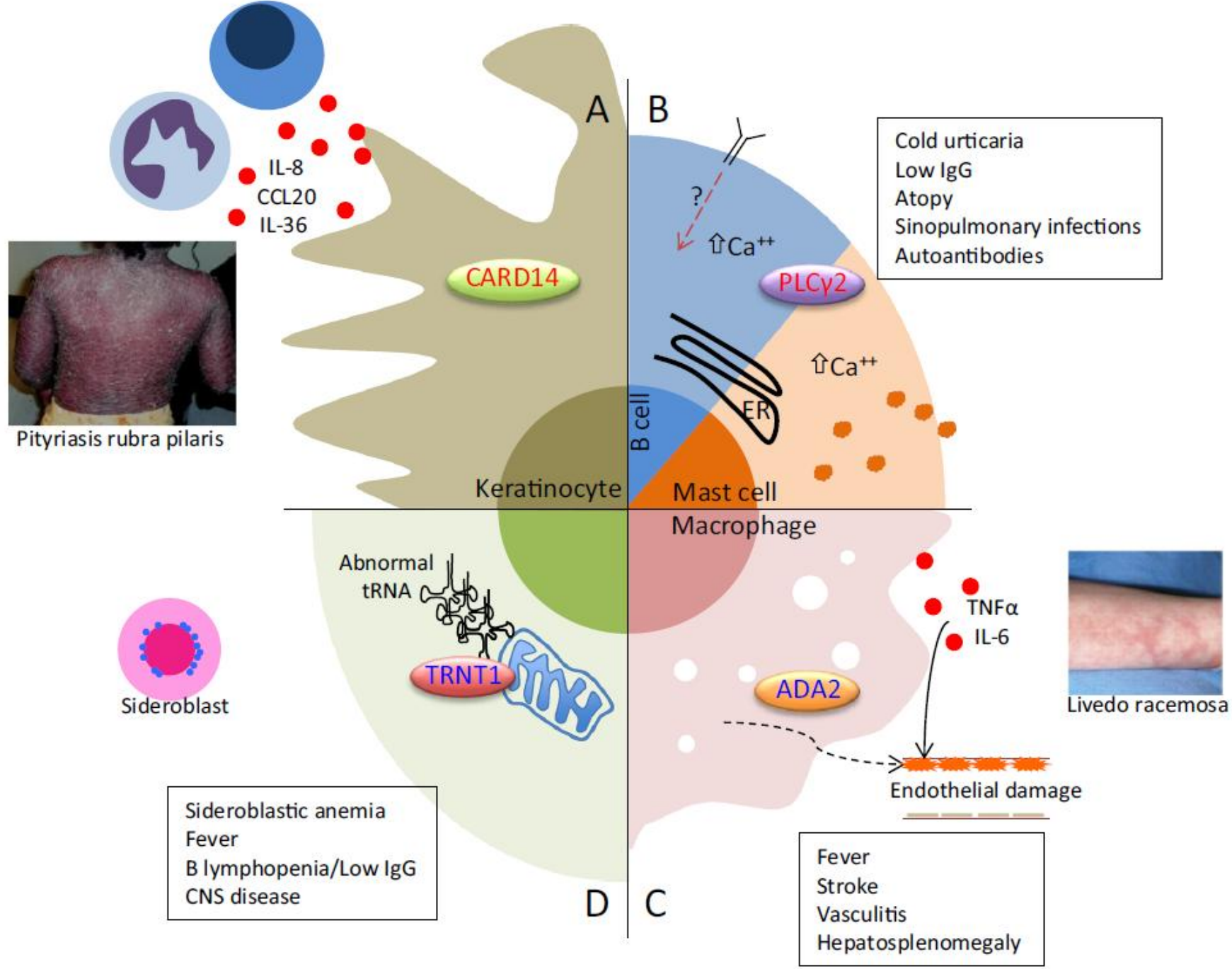


Déséquilibre des antagonistes endogènes:
Mutations *IL1RN, IL36RN*

Adapted from Holzinger, Nat Rev Rheum, 2015

Hématopoïèse Humaine

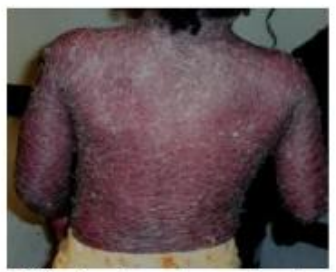




Canna, Semin Immunopathol, 2015

Traitemements topiques?

Anti IL17/23? *(psoriasis)*



Pityriasis rubra pilaris

IL-8
CCL20
IL-36

A

CARD14

Keratinocyte

B

?

⇧Ca++

PLCγ2

Cold urticaria
Low IgG
Atopy
Sinopulmonary infections
Autoantibodies

-Stabilisateur du mastocyte?
-Antihistaminiques?
-Inhibiteurs de tyrosine kinase?

B cell

ER

⇧Ca++

Mast cell

Macrophage

Abnormal tRNA

TRNT1

Sideroblast

-Allogreffe de moelle
-Agents hypométhylants
=>azacitidine (VIDAZA)

Sideroblastic anemia
Fever
B lymphopenia/Low IgG
CNS disease

D

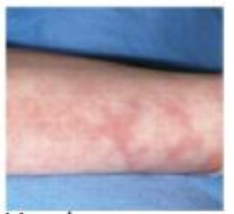
C

TNFα
IL-6

ADA2

Endothelial damage

Fever
Stroke
Vasculitis
Hepatosplenomegaly

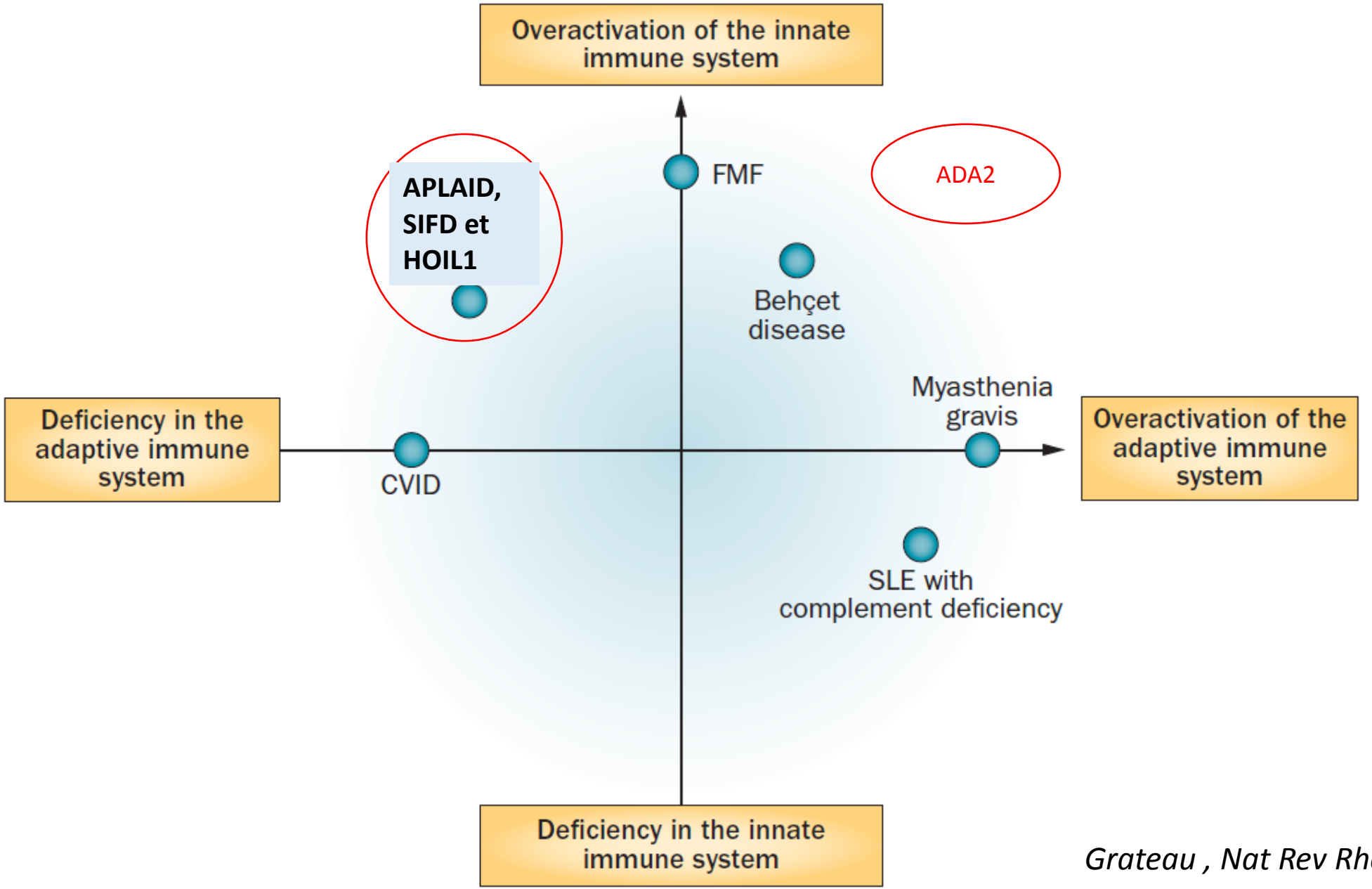


Livedo racemosa

Anti TNFα
Anti IL6

Canna, Semin Immunopathol, 2015

DEFICIT IMMUNITAIRE ET MAI



Grateau , Nat Rev Rheum 2013

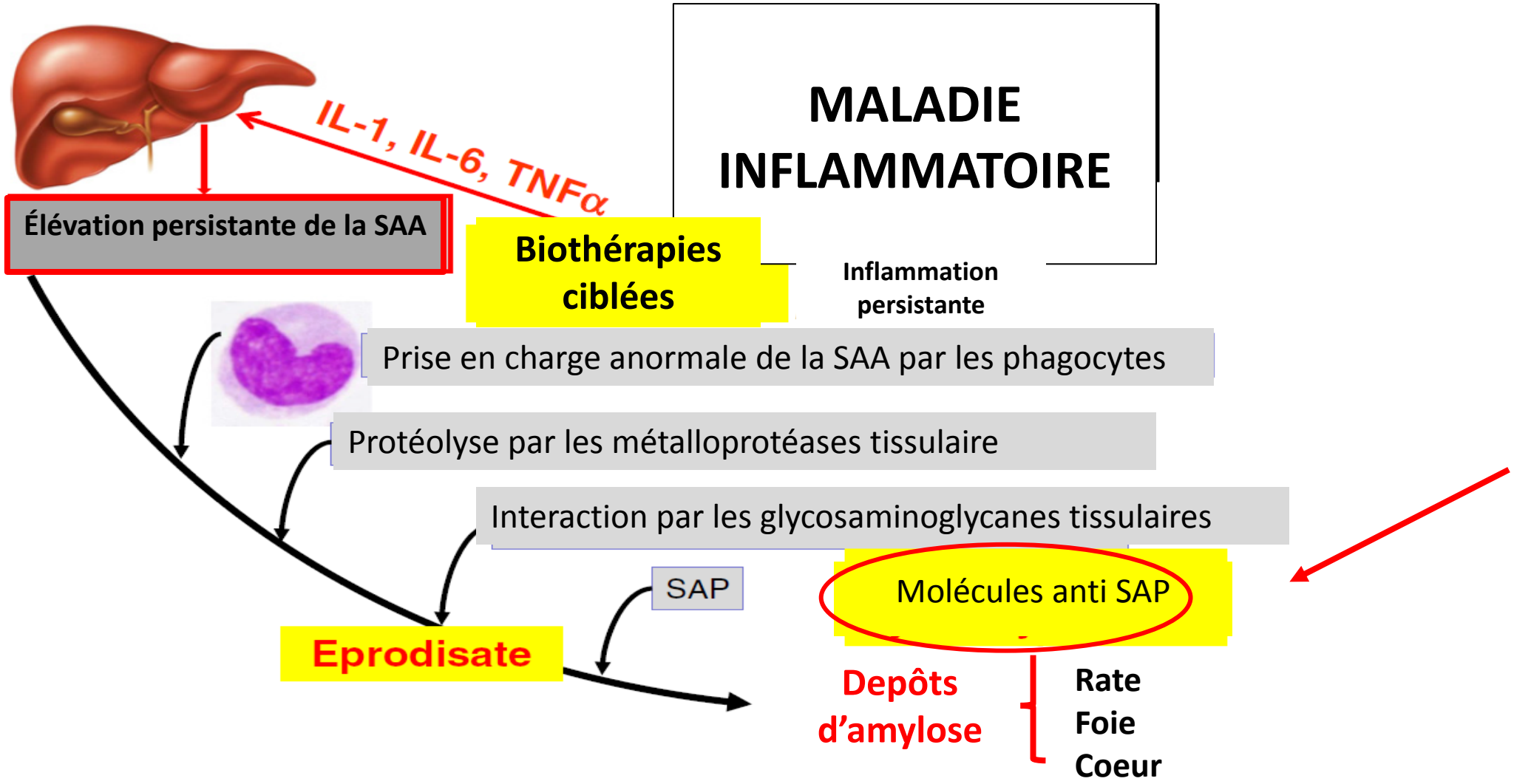
DEFICIT IMMUNITAIRE ET MAI

- **Pathologies: mutations de *CECR1, HOIL1, PLCG2,TRNT1***
- **Peu de données publiées**
- **Efficacité des anti TNFα dans les déficit en ADA2**
- **=>voir des anti IL6 (si il6 élevée ds sg)**

- **Si DICV:**
  - **Discuter IgIV si infections fréquentes**
  - **Chez l'adulte: Bactrim fort 1 cp x3/sem**

AMYLOSE AA

BUT DU TRAITEMENT: CONTROLER L'INFLAMMATION



Obici, Autoimmunity Rev, 2012

AMYLOSE AA: NOUVEAUTES THERAPEUTIQUES

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component

Duncan B. Richards, D.M., Louise M. Cookson, B.Sc., Alienor C. Berges, Pharm.D., Sharon V. Barton, M.Sc., Thirusha Lane, R.N., M.Sc., James M. Ritter, D.Phil., F.Med.Sci., Marianna Fontana, M.D., James C. Moon, M.D., Massimo Pinzani, M.D., Ph.D., Julian D. Gillmore, M.D., Ph.D., Philip N. Hawkins, Ph.D., F.Med.Sci., and Mark B. Pepys, Ph.D., F.R.S.

Juillet 2015: Anticorps anti composant P (SAP)
15 patients dont 2 AAA
Efficacité dans 1 cas d'AAA/2

DICV, mutation hétérozygote NLRP12 et amylose AA

Clinical Immunology (2014) 154, 105–111

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

BRIEF COMMUNICATION

Novel *NLRP12* mutations associated with intestinal amyloidosis in a patient diagnosed with common variable immunodeficiency

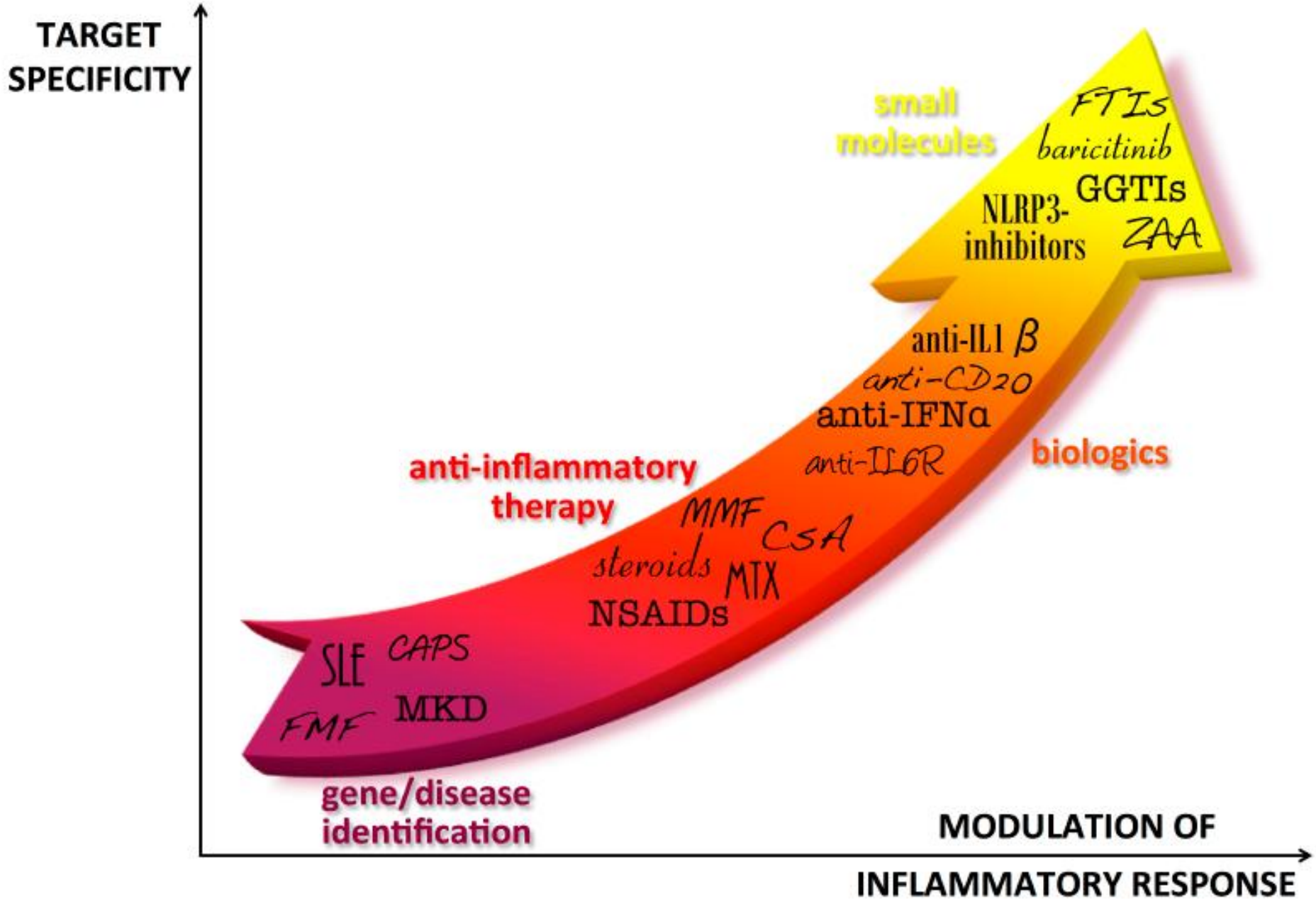
Stephan Borte[a,b,c,*], Mehmet Halil Celiksoy[d], Volker Menzel[b], Ozan Ozkaya[e], Fatma Zeynep Ozen[f], Lennart Hammarström[b], Alisan Yildiran[d]

Received 21 April 2014; accepted with revision 16 July 2014

CONCLUSION: Nouvelles cibles thérapeutiques MAI:

- **Inflammasomopathies**
  - **Anti IL18**
  - **Peptides anti NLRP3: BHB et MCC950**
  - **HIGD: bloquer la voie du mévalonate: inhibiteurs de farnesyl transferase**
- **Interféronopathies**
  - **Anti JAK2 (Ruxolinib, Baricitinib)**
  - **Anti INFα (Sifalimumab, Rontalizumab);** *également dans le déficit en NLRC4*

- **Amylose AA?**
  - **Prévention+++++**
  - **Biothérapies (anti IL1, anti IL6, petites molécules)**



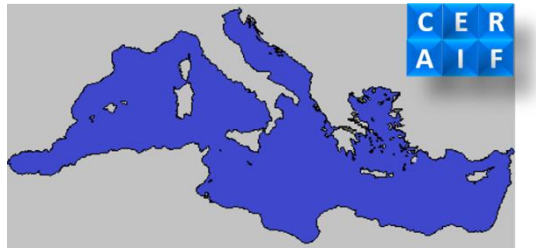
Marcuzzi, 2015, Int J Mol Sci

CONCLUSIONS

	IL Y A 20 ANS	2015
NOSOLOGIE	INCONNNUE	MALADIES **AUTO** INFLAMMATOIRES
PHYSIOPATHOLOGIE	INCONNUE	MUTATIONS POUR BEAUCOUP DE MAI
TRAITEMENT	COLCHICINE	COLCHICINE Inhibiteurs Il-1beta Autres biothérapies

Régime cétogénique anti NLRP3?

MERCI DE VOTRE ATTENTION



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