Bernhard RYFFEL is MD, PhD, INEM, UMR7355, CNRS, University, Orleans, France, bryffel@cnrs-orleans.fr +33 6 29 15 22 87, https://www.univ-orleans.fr/es/inem

Medical education in Bern and Geneva, MD 1978. PhD 1984 and FMH in pathology 1988 in Basel. Positions held: 1974 Immunology University of Bern, 1979 Pharmacology Sandoz Pharma Basel, 1991 University of Zurich, Pharmacology-Toxicology, 1995, Professor of Immunology University Cape Town, RSA. Since 2001 Director of research, CNRS Immunology, Orleans, France with active research, and advisor of several pharmaceutical companies. Founder of Artimmune SAS and Phenotec AG.



Research: Mechanisms of inflammation, especially respiratory inflammation, fibrosis, emphysema and COPD, but also in skin, hepatic, intestinal, renal and CNS inflammation. Cell death, innate immune danger sensing and cGAS/STING, ROS and Inflammasome activation in models of human inflammatory diseases and tumor development, role of microbiome, metabolome, neuroinflammation/degeneration and ageing. Role of TNF and IL-1 members, in cell death and IL-33 and T2 / T17 polarization and differentiation. **PB drug candidate** Stable butyrate to treat chronic lung inflammatory disease.

Recent publications (>550, HF>100)

Lopes GAO, Lima BHF, Freitas CS, Soriani FM, Cassali GD, Ryffel B, Machado FS, Russo RC. Opposite effects of systemic and local conditional CD11c+ myeloid cell depletion during bleomycin-induced inflammation and fibrosis in mice. Immun Inflamm Dis. 2024 PMID: 39582275;

Messaoud-Nacer Y, Culerier E, Rose S, Maillet I, Boussad R, Veront C, Savigny F, Malissen B, Radzikowska U, Sokolowska M, da Silva GVL, Edwards MR, Jackson DJ, Johnston SL, Ryffel B, Quesniaux VF, Togbe D. STING-dependent induction of neutrophilic asthma exacerbation in response to house dust mite. Allergy. 2024 Oct 28. doi: 10.1111/all.16369.

Dimitrov G, Ryffel B, Togbe D, Quesniaux V. cGAS-STING DNA-sensing in inflammatory bowel diseases. Trends Mol Med. 2024: PMID: 39448330.

Schlecht-Louf G, Federici S, Ryffel B, Russo RC. Editorial: The chemokine system in epithelial immunity. Front Immunol. 2024:

PMCID: PMC11390664.

Varela Martins T, Silva de Melo BM, Toller-Kawahisa JE, Silva GV, Anibal-Silva CE, Paiva IM, Publio GA, Rosa MH, da Silva Souza C, Zamboni DS, Cunha FQ, Cunha TM, Ryffel B, Riteau N, Alves-Filho JC. The DNA sensor AIM2 mediates psoriasiform inflammation by inducing type 3 immunity. JCI Insight 2024 doi: 10.1172/jci.insight.171894. Epub ahead of print. PMID: 39352743.

Devulder J, Barrier M, Carrard J, Amniai L, Plé C, Marquillies P, Ledroit V,Ryffel B, Tsicopoulos A, de Nadai P, Duez C. Pulmonary Administration of TLR2/6 Agonist after Allergic Sensitization Inhibits Airway Hyper-Responsiveness and Recruits Natural Killer Cells in Lung Parenchyma. Int J Mol Sci. 2024; PMCID: PMC11394962.

Muela-Zarzuela I, Ryffel et al. <u>NLRP1 inflammasome promotes senescence and senescenceassociated secretory phenotype.</u> Inflamm Res. 2024. PMID: 38907167.

Mbalaviele G, Ryffel B. Editorial: Inflammasomes in human diseases and metabolism. Front Immunol. 2024. doi:10.3389/fimmu.2024.1420303. PMID: 38840909;

Nascimento M, Huot-Marchand S, Fanny M, Straube M, Le Bert M, Savigny F, Apetoh L, Van Snick J, Trovero F, Chamaillard M, Quesniaux VFJ, Ryffel B, Gosset P, Gombault A, Riteau N, Sokol H, Couillin I. NLRP6 controls pulmonary inflammation from cigarette smoke in a gut microbiota-dependent manner. Front Immunol. 2023: 10.3389/fimmu.2023.1224383. PMID: 38146368.

Bugaut H, El Morr Y, Mestdagh M, Darbois A, Paiva RA, Salou M, Le Gac AL, Ryffel B, Montagutelli X, Lantz O, Legoux F. A conserved transcriptional program for MAIT cells across mammalian evolution. J Exp Med. 2024 Feb 5;221(2):e20231487. doi: 10.1084/jem.20231487

Cutrin JC, Alves-Filho JC, Ryffel B. Editorial: Sepsis: studying the immune system to highlight biomarkers for diagnosis, prognosis and personalized treatments. Front Immunol. 2023 22;14:1325020. doi: 10.3389/fimmu.2023.1325020.

Russo RC, Quesniaux VFJ, Ryffel B. Homeostatic chemokines as putative therapeutic targets in idiopathic pulmonary fibrosis. Trends Immunol. 2023 Nov 9:S1471-4906(23)00210-7. doi: 10.1016/j.it.2023.10.003.

Carignon S, De Moura Rodrigues D, Gosset D, Culerier E, Huot-Marchand S, Savigny F, Kaya E, Quesniaux V, Gombault A, Couillin I, Ryffel B, Le Bert M, Riteau N. Lung inflammation and interstitial fibrosis by targeted alveolar pithelial type I cell death. Front Immunol. 2023. 14:1261483. doi: 10.3389/fimmu.2023.1261483.

Leinardi R, Pochet A, Uwambayinema F, Yakoub Y, Quesniaux V, Ryffel B, Broz P, Pavan C, Huaux F. Gasdermin D membrane pores orchestrate IL- 1α secretion from necrotic macrophages after NFS-rich silica exposure. Arch Toxicol. 2023.;97(4):1001-1015. doi: 10.1007/s00204-023-03463-x.

Baldrighi M, Doreth C, Li Y, Zhao X, Warner EF, Chenoweth H, Kishore K, Latz E, de Cárcer G, Malumbres M, **Ryffel B**, Bryant CE, Liu J, Lilley KS, Mallat Z, Li X.J PLK1 inhibition dampens NLRP3 inflammasome-elicited response in inflammatory disease models. J Clin Invest. 2023 Sep 12:e162129. doi: 10.1172/JCI162129.

Bergant V, Schnepf D, de Andrade Krätzig N, Hubel P, Urban C, Engleitner T, Dijkman R, **Ryffel B**, Steiger K, Knolle PA, Kochs G, Rad R, Staeheli P, Pichlmair A. mRNA 3'UTR lengthening by alternative polyadenylation attenuates inflammatory responses and correlates with virulence of Influenza A virus. Nat Commun. 2023 Aug 15;14(1):4906. doi: 10.1038/s41467-023-40469-6

de Melo BMS, Veras FP, Zwicky P, Lima D, Ingelfinger F, Varela T, Nakaya HI, da Silva Souza C, Cunha FQ, Cunha TM, Ryffel B, Becher B, Alves-Filho JC. S100A9 drives the chronification of psoriasiform inflammation by inducing IL-23/type 3 immunity. J Invest Dermatol. 2023 Mar 13:S 0022-202X(23)01825-0. doi: 10.1016/j.jid.2023.02.026.

Leinardi R, Pochet A, Uwambayinema F, Yakoub Y, Quesniaux V, Ryffel B, Broz P, Pavan C, Huaux F. Gasdermin D membrane pores orchestrate IL- 1α secretion from necrotic macrophages after NFS-rich silica exposure. Arch Toxicol. 2023 Apr;97(4):1001-1015. doi: 10.1007/s00204-023-03463-x.

Corrêa RO, Castro PR, Moser R, Ferreira CM, Quesniaux VFJ, Vinolo MAR, Ryffel B. Butyrate: Connecting the gut-lung axis to the management of pulmonary disorders. Front Nutr. 2022 Oct 20;9:1011732. doi: 10.3389/fnut.2022.1011732.

Bauer A, Pachl E, Hellmuth JC, Ryffel B, Schubert B, Hilgendorff A. Proteomics reveals antiviral host response and NETosis during acute COVID-19 in high-risk patients. Biochim Biophys Acta Mol Basis Dis. 2022. doi: 10.1016/j.bbadis.2022.166592.

Lecron JC, Charreau S, Jégou JF, Bernard FX, Ryffel B, Morel F. IL-17 and IL-22 are pivotal cytokines to delay wound healing of <i>S. aureus and P. aeruginosa</i> infected skin. Front Immunol. 2022 Oct 7;13:984016. doi: 10.3389/fimmu.2022.984016. PMID: 36275755; PMCID: PMC9585169.

Cordier-Dirikoc S, Pedretti N, Garnier J, Clarhaut-Charreau S, Ryffel B, Morel F, Bernard FX, Hamon de Almeida V, Lecron JC, Jégou JF. Dermal fibroblasts are the key sensors of aseptic skin inflammation through interleukin 1 release by lesioned keratinocytes. Front Immunol. 2022 Oct 3;13:984045. doi: 10.3389/fimmu.2022.984045.

Hrdý J, Couturier-Maillard A, Boutillier D, Lapadatescu C, Blanc P, Procházka J, Pot B, Ryffel B, Grangette C, Chamaillard M. Oral supplementation with selected Lactobacillus acidophilus triggers IL-17-dependent innate defense response, activation of innate lymphoid cells type 3 and improves colitis. Sci Rep. 2022 Oct 20;12(1):17591. doi: 10.1038/s41598-022-21643-0

Secher T, Couturier A, Huot L, Bouscayrol H, Grandjean T, Boulard O, Hot D, Ryffel B, Chamaillard M. A protective role of NOD2 on oxazolone-induced intestinal inflammation through IL-12-mediated signaling pathway. J Crohns Colitis. 2022 Aug 2:jjac106. doi: 10.1093/ecco-jcc/jjac106.

Roberts LB, Berkachy R, Wane M, Patel DF, Schnoeller C, Lord GM, Gounaris K, Ryffel B, Quesniaux V, Darby M, Horsnell WGC, Selkirk ME. Differential Regulation of Allergic Airway Inflammation by Acetylcholine. Front Immunol. 2022; doi: 10.3389/fimmu.2022.893844.

N, Messaoud-Nacer Y, Maillet I, Ledru A, Quesniaux VFJ, Ryffel B, Horsnell W, Végran F, Apetoh L, Togbe D. NLRP6 negatively regulates type 2 immune responses in mice. Allergy. 2022.77(11):3320-3336. doi: 10.1111/all.15388.

Galli G, Vacher P, Ryffel B, Blanco P, Legembre P. Fas/CD95 Signaling Pathway in Damage-Associated Molecular Pattern (DAMP)-Sensing Receptors. Cells. 2022; 24;11(9):1438. doi: 10.3390/cells11091438.

Lima C, Andrade-Barros AI, Bernardo JTG, Balogh E, Quesniaux VF, Ryffel B, Lopes-Ferreira M. Natterin-Induced Neutrophilia Is Dependent on cGAS/STING Activation via Type I IFN Signaling Pathway. Int J Mol Sci. 2022; 25;23(7):3600. doi: 10.3390/ijms23073600.

Sedda D, Mackowiak C, Pailloux J, Culerier E, Dudas A, Rontani P, Erard N, Lefevre A, Mavel S, Emond P, Foucher F, Le Bert M, Quesniaux VFJ, Mihatsch MJ, Ryffel B, Erard-Garcia M. Deletion of <i>Mocos</i> Induces Xanthinuria with Obstructive Nephropathy and Major Metabolic Disorders in Mice. Kidney360. 2021; 17;2(11):1793-1806. doi: 10.34067/KID.0001732021.

Bruchard M, Geindreau M, Perrichet A, Truntzer C, Ballot E, Boidot R, Racoeur C, Barsac E, Chalmin F, Hibos C, Baranek T, Paget C, Ryffel B, Rébé C, Paul C, Végran F, Ghiringhelli F. Recruitment and activation of type 3 innate lymphoid cells promote antitumor immune responses. Nat Immunol. 2022 Feb;23(2):262-274. doi: 10.1038/s41590-021-01120-y.

Li C, Qiu M, Chang L, Qi J, Zhang L, Ryffel B, Deng L. The osteoprotective role of USP26 in coordinating bone formation and resorption. Cell Death Differ. 2022 Jun;29(6):1123-1136. doi: 10.1038/s41418-021-00904-x.

Benoit-Lizon I, Jacquin E, Rivera Vargas T, Richard C, Roussey A, Dal Zuffo L, Martin T, Melis A, Vinokurova D, Shahoei SH, Baeza Garcia A, Pignol C, Giorgiutti S, Carapito R, Boidot R, Végran F, Flavell RA, Ryffel B, Soulas-Sprauel P, Lawrence T, Apetoh L. CD4 T cell-intrinsic STING signaling controls the differentiation and effector functions of TH1 and TH9 cells. J Immunother Cancer. 2022 Jan;10(1):e003459. doi: 10.1136/jitc-2021-003459.

Yonekura S, Terrisse S, Alves Costa Silva C, Lafarge A, Mansouri G, Ugolini S, Quiniou V, Berrard S, Ryffel B, Kepp O, Kroemer G, Routy B, Lordello L, Bani MA, Segata N, Yengej FY, Clevers H, Scoazec JY, Pasolli E, Derosa L, Zitvogel L. Cancer Induces a Stress Ileopathy Depending on β -Adrenergic Receptors and Promoting Dysbiosis that Contributes to Carcinogenesis. Cancer Discov. 2022 Apr 1;12(4):1128-1151. doi: 10.1158/2159-8290.CD-21-0999. PMID: 34930787.

Nascimento DC, Viacava PR, Ferreira RG, Damaceno MA, Zamboni DS, Fonseca DM, Cunha TM, Quesniaux V, Linden J, Cunha FQ, Ryffel B, Alves-Filho JC. Sepsis expands a CD39+plasmablast population that promotes immunosuppression via adenosine-mediated inhibition of macrophage antimicrobial activity. Immunity. 2021. doi: 10.1016/j.immuni.2021.08.005.

Dalloul Z, Best M, Chenuet P, Togbé D, Gador M, Ryffel B, Quesniaux V, Fazilleau N, Cogné M. Bromodomain and extraterminal (BET) protein inhibition of IgG/IgE production in murine B cells is counter-balanced by a strong Th2 bias. Clin Transl Immunology. 2021. doi: 10.1002/cti2.1280.

Uyanik B, Goloudina AR, Akbarali A, Grigorash BB, Lagorgette L, Hadi T, Baidyuk EV, Sakai H, Tessarollo L, Ryffel B, Mazur SJ, Lirussi F, Garrido C, Appella E, Demidov ON. Inhibition of the DNA damage response phosphatase PPM1D reprograms neutrophils to enhance anti-tumor immune responses. Nat Commun. 2021. doi: 10.1038/s41467-021-23330-6

Mackowiak C, Marchiol T, Stoeger T, Schiller HB, Sirard JC, Le Bert M, Couillin I, Quesniaux VFJ, Togbe D, Ryffel B. Chronic Pseudomonas aeruginosa Lung Infection Is IL-1R Independent, but Relies on MyD88 Signaling. Immunohorizons. 2021. doi: 10.4049/immunohorizons.2000095.

Chetty A, Darby MG, Vornewald PM, Filz A, Ritter M, McSorley HJ, Masson L, Smith K, Brombacher F, O'Shea MK, Cunningham AF, Ryffel B, Oudhoff MJ, Dewals BG, Layland LE, Horsnell WGC. Il4ra-independent vaginal eosinophil accumulation following helminth infection exacerbates epithelial ulcerative pathology of HSV-2 infection. Cell Host Microbe. 2021. doi: 10.1016/j.chom.2021.02.004.

Alves-Filho JC, Marcel Silva Melo B, Ryffel B. MMP-9 Mediates Cross-Talk between Neutrophils and Endothelial Cells in Psoriasis. J Invest Dermatol. 2021. doi: 10.1016/j.jid.2020.09.006.

Nehmar R, Fauconnier L, Alves-Filho J, Togbe D, DeCauwer A, Bahram S, Le Bert M, Ryffel B, Georgel P. Aryl hydrocarbon receptor (Ahr)-dependent II-22 expression by type 3 innate lymphoid cells control of acute joint inflammation. J Cell Mol Med. 2021. doi: 10.1111/jcmm.

Roberts LB, Schnoeller C, Berkachy R, Darby M, Pillaye J, Oudhoff MJ, Parmar N, Mackowiak C, Sedda D, Quesniaux V, Ryffel B, Vaux R, Gounaris K, Berrard S, Withers DR, Horsnell WGC, Selkirk ME. Acetylcholine production by group 2 innate lymphoid cells promotes mucosal immunity to helminths. Sci Immunol. 2021: eabd0359. doi: 10.1126/sciimmunol.abd0359.

Navarro-Pando JM, Alcocer-Gómez E, Castejón-Vega B, Ryffel B, Cordero MD. Inhibition of the NLRP3 inflammasome prevents ovarian aging. Sci Adv. 2021:eabc7409. doi:10.1126/sciadv.abc7409.

Douguet L, Janho Dit Hreich S, Benzaquen J, Seguin L, Juhel T, Dezitter X, Duranton C, Ryffel B, Kanellopoulos J, Adriouch S, Ghinet A, Hofman P, Vouret-Craviari V. A small-molecule P2RX7 activator promotes anti-tumor immune responses and sensitizes lung tumor to immunotherapy. Nat Commun. 2021 Jan 28;12(1):653. doi: 10.1038/s41467-021-20912-2.

Schricke C, Lacerda-Queiroz N, Meda M, Nascimento M, Huot-Marchand S, Da Gama Monteiro F, Ryffel B, Gombault A, Le Bert M, Couillin I, **Riteau N.** Protective Role of the Nucleic Acid Sensor STING in Pulmonary Fibrosis. Front Immunol. 2021 Jan 8;11:588799. doi: 10.3389/fimmu.2020.588799

Wiegman CH, Li F, Ryffel B, Togbe D, Chung KF. Oxidative Stress in Ozone-Induced Chronic Lung Inflammation and Emphysema: A Facet of Chronic Obstructive Pulmonary Disease. Front Immunol. 2020 Sep 2;11:1957. doi: 10.3389/fimmu.2020.01957.

Di Domizio J, Chenuet P, Fries A, Ryffel B, Gilliet M. The commensal skin microbiota triggers type I IFN-dependent innate repair responses in injured skin. Nat Immunol. 2020 Jul 13. doi: 10.1038/s41590-020-0721-6. Nat Immunol. 2020. PMID: 32661363

Roberti MP, Yonekura S, Duong CPM, Picard M, Ferrere G, Ryffel B, Raoult D, Eggermont A, Vanden Berghe T, Ghiringhelli F, Vandenabeele P, Kroemer G, Zitvogel L. Chemotherapy-induced ileal crypt apoptosis and the ileal microbiome shape immunosurveillance and prognosis of proximal colon cancer. *Nat Med.* 2020 May 25. doi: 10.1038/s41591-020-0882-8.

Michaudel C, Bataille F, Maillet I, Fauconnier L, Colas C, Sokol H, Straube M, Couturier-Maillard A, Dumoutier L, van Snick J, Quesniaux VF, Togbe D, Ryffel B. Ozone-Induced Aryl Hydrocarbon Receptor Activation Controls Lung Inflammation via Interleukin-22 Modulation. Front Immunol. 2020 Feb 25;11:144. Doi: 10.3389/fimmu.2020.00144.

Nascimento M, Gombault A, Lacerda-Queiroz N, Panek C, Bourinet M, Le Bert M, Riteau N, Ryffel B, Quesniaux VFJ, Couillin I. Self-DNA release and STING-dependent sensing drives inflammation to cigarette smoke in mice. Sci Rep. 2019 Oct 16;9(1):14848. doi: 10.1038/s41598-019-51427-y.

Sokolowska M, Quesniaux VFJ, Akdis CA, Chung KF, Ryffel B, Togbe D. Acute Respiratory Barrier Disruption by Ozone Exposure in Mice. Front Immunol. 2019 Sep 13;10:2169G,

Tidjani Alou M, Liu P, Ryffel B, Segata N, Derosa L, Kroemer G, Zitvogel L. Ketogenic diet and ketone bodies enhance the anticancer effects of PD1 blockade. JCI Insight. 2020 Dec 15:145207. doi: 10.1172/jci.insight.145207.

Togbe D, Benmerzoug S, Jacobs M, Ryffel B, Quesniaux VFJ. Silica-related, diseases in the modern world: A role for self-DNA sensing in lung inflammatory diseases. Allergy. 2020 Nov;75(11):3009-3010. doi: 10.1111/all.14463.

Reverchon F, de Concini V, Larrigaldie V, Benmerzoug S, Briault S, Togbé D, Ryffel B, Quesniaux VFJ, Menuet A. Hippocampal interleukin-33 mediates neuroinflammation-induced cognitive impairments. J Neuroinflammation. 2020 Sep 11;17(1):268. doi: 10.1186/s12974-020-01939-6.

Marín-Aguilar F, Lechuga-Vieco AV, Alcocer-Gómez E, Varela-López A, Quiles JL, Ryffel B, Flores I, Bullón P, Ruiz-Cabello J, Cordero MD. NLRP3 inflammasome suppression improves longevity and prevents cardiac aging in male mice. *Aging Cell.* 2020 Jan;19(1):e13050. doi: 10.1111/acel.13050.

Duez C, Gross B, Marquillies P, Ledroit V, Ryffel B, Glineur C. Regulation of IL-33 Production in Endothelial Cells via Kinase Activation and Fas/CD95 Upregulation. Arterioscler Thromb Vasc Biol. 2020 Nov;40(11):2619-2631. doi: 10.1161/ATVBAHA.120.314832.

Luiz JPM, Toller-Kawahisa JE, Viacava PR, C,Cunha TM, Cunha FQ, Quesniaux V, Ryffel B, Alves-Filho JC. MEK5/ERK5 signaling mediates IL-4-induced M2 macrophage differentiation through regulation of c-Myc expression. J Leukoc Biol. 2020 Oct;108(4):1215-1223. doi: 10.1002/JLB.1MA0520-016R.

Cañadas-Lozano D, Marín-Aguilar F, Castejón-Vega B, Ryffel B, Navarro-Pando JM, Ruiz-Cabello J, Alcocer-Gómez E, Bullón P, Cordero MD. Blockade of the NLRP3 inflammasome improves metabolic health and lifespan in obese mice. Geroscience 42:715-725 (2020) doi: 10.1007/s11357-019-00151-6.

Legoux F, Bellet D, Ryffel B, Balvay A, Foussier A, Sarkis M, El Marjou A, Schmidt F, Rabot S, Lantz O. Microbial metabolites control the thymic development of mucosal-associated invariant T cells. Science. 2019 Aug 29. doi:10.1126/science.aaw2719.

Benmerzoug S, Ryffel B, Togbe D, Quesniaux VFJ. Self-DNA Sensing in Lung Inflammatory Diseases. Trends Immunol. 2019 Aug;40(8):719-734. doi: 10.1016/j.it.2019.06.001.

Benmerzoug S, Bounab B, Rose S, Gosset D, Biet F, Cochard T, Fauconnier L, Horsnell WGC, Ryffel B, Togbe D, Quesniaux VFJ. Sterile Lung Inflammation Induced by Silica Exacerbates Mycobacterium tuberculosis Infection via STING-Dependent Type 2 Immunity.
Cell Rep. 2019;27(9):2649-2664.e5.doi: 10.1016/j.celrep.2019.04.110.

Benmerzoug S, Rose S, Bounab B, Gosset D, Laurenceau D, Ryffel B, Apetoh L, Kiziltunc A, Uslu H, Albez FS, Akgun M, Togbe D, Quesniaux VFJ. STING-dependent sensing of self-DNA drives silicainduced lung inflammation. Nat Commun. 2018 Dec 6;9(1):5226. doi: 10.1038/s41467-018-07425-1.

Michaudel C, Mackowiak C, Maillet I, Akdis C, Sokolowska M, Tan HT, Quesniaux VF, Ryffel B, Togbe D. Ozone exposure induces respiratory barrier biphasic injury and inflammation controlled by IL-33. J Allergy Clin Immunol. 2018 Sep;142(3):942-958. doi: 10.1016/j.jaci.2017.11.044.

Holze C, Michaudel C, Mackowiak C, Haas DA, Benda C, Hubel P, Pennemann FL, Schnepf D, Wettmarshausen J, Braun M, Leung DW, Amarasinghe GK, Perocchi F, Staeheli P, Ryffel B, Pichlmair A. Oxeiptosis, a ROS-induced caspase-independent apoptosis-like cell-death pathway. Nat Immunol. 2017 Dec 18. PubMed PMID: 29255269.