

COMBADIÈRE Christophe, PhD

Directeur de Recherche Inserm / Senior Scientist Inserm

Directeur du CIMI-Paris / *Head of CIMI-Paris*

Chef d'Equipe / Team Leader **Les Chimiokines dans les pathologies et maladies inflammatoires / Chemokines in Pathologies and Inflammation**

Bio

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Formation / Education

1993 PhD in biochemistry and cell biology, University Paris Sud- Orsay, France.
2003 Habilitation à diriger des Recherches (HDR), University Paris Diderot, Paris, France.

Expérience professionnelle antérieure / Past Professional experience

2014 - Head of Research Center CIMI-Paris
2008-2013 Team Leader, Laboratory of "Immunité et Infection"-INSERM UMR-S945 (Dir. : Prof . D. Mazier), Faculté de Médecine, Paris 75013 (Theme of research: Chemokines in Pathologies and Inflammation)
2005-2007 Team Leader, Senior Scientist, Laboratory of Cellular Immunology - INSERM U543 (Dir. Pr. Debré), Faculté de Médecine, Paris 75013 (Theme of research: Role of chemokine receptors in the immune response)
2001-2005 Principal Investigator, Laboratory of Cellular Immunology - INSERM U543 (Dir. Pr. Debré), Faculté de Médecine, Paris 75013 (Theme of research: Role of chemokine receptors in the immune response)
1997-2001 Principal Investigator, INSERM U479 (dir; : Pr. Gougerot-Pocidallo), CHU. X. Bichat, Paris 75018 (Theme of research: Role of chemokine receptors in the inflammatory response)
1993-1997 Postdoctoral fellow, Laboratory of Host Defenses (Chief of section : Dr. P. M. Murphy), NIAID, NIH, Bethesda, Maryland, USA (Theme of research: Characterization of new chemokine receptors)

Distinctions - Titres honorifiques / Honors and Awards

2011 Inserm Award for career excellence
2007 NRJ Foundation award.
2003 Senior Scientist – DR2 (Director of research) Inserm
2000 Dolph Adams Award for the most cited research paper published from 1995-1999 in Journal of Leukocyte Biology.

Recherche / Research

Mots-clés / Keywords: VF- Immunologie-Inflammation-monocyte-Chimiokine-migration-adhesion-signalisation intracellulaire / VGB- *Immunology-Inflammation-monocyte-Chemokine-migration-adhesion-Signal transduction pathways*

Programmes en cours / Current Research

L'inflammation est une réaction immunitaire commune à de nombreuses pathologies humaines. L'une de ses principales caractéristiques est le déploiement de cellules immunitaires au niveau du site lésionnel. Nos travaux portent sur l'identification de molécules responsables de cette redistribution bloquant spécifiquement les sous-populations cellulaires conduisant aux processus pathogéniques tout en conservant intactes celles nécessaires à la migration et aux fonctions des leucocytes responsables de l'immunité protectrice.

Les chimiokines (CK) sont des médiateurs de l'inflammation et de l'immunité qui permettent non seulement une migration rapide et coordonnée en réponse à des signaux de dangers mais aussi contrôlent diverses fonctions cellulaires immunitaires. Les CK et leurs récepteurs (CKR) sont centraux à la réponse inflammatoire et sont ainsi des cibles prioritaires pour l'industrie pharmaceutique.

Notre programme de recherche vise à établir les preuves que les thérapies basées sur les CK seraient une excellente stratégie pour les traitements des maladies inflammatoires. Notre démarche s'appuie sur quatre axes de recherche ; 1) l'analyse des relations structures/fonctions des CK et CKR inflammatoires, 2) des études *ex vivo* qui déterminent les rôles des CK/CKR sur des sous-populations leucocytaires dans les pathologies humaines, 3) des études *in vivo* qui analysent les rôles of CK/CKR dans des modèles murins de pathologies inflammatoires, et 4) le développement d'outils thérapeutiques basés sur les CK/CKR.

Ce programme de recherche qui s'inscrit dans une démarche allant de l'analyse moléculaire à la valorisation de nouveaux outils thérapeutiques en démontrant la pertinence des traitements chimiokiniques dans des modèles murins précliniques, s'appuie sur la découverte de petits peptides antagonistes qui ont déjà démontré leurs fortes capacités à limiter l'infiltration monocytaire dans les organes.

Inflammation is a hallmark of numerous human diseases and a key aspect of it is trafficking of immune cells into and out of the specific injured tissues. Thus, the challenge for the future will be to identify the trafficking molecules that will most specifically inhibit the key subsets of cells that drive disease processes without affecting the migration and function of leukocytes required for protective immunity. Chemokines (CK) are typical immune and inflammatory mediators that not only allow a rapid and appropriate leukocyte migration to emergency signals but also control cellular responses. CK and their receptors (CKR) are central to the inflammatory process and are thus attractive targets for the pharmaceutical industry.

Our research program aims to establish the evidence that the CK-based therapy could become a new way of treatment of inflammatory diseases. It includes four approaches; 1) structural and functional analysis of inflammatory CK and CKR, 2) ex vivo studies that analyze the role of CK/CKR on subsets of leukocytes in human diseases, 3) in vivo studies that characterize the role of CK/CKR in inflammatory mouse models, and 4) the development of CK/CKR-based therapeutic tools.

The project pipeline, from molecular analysis, proof-of-principle evaluation in murine models to valorization, is taking advantage of new short peptide-based antagonist candidates that have already shown strong efficacy in limiting monocyte infiltration in organs.

Réalisations représentatives / Major achievements

- Caractérisation du rôle des RCK dans l'athérosclérose, l'infection VIH, les cancers et la dégénérescence maculaire liée à l'âge / *Characterisation of the role of the RCK in atherosclerosis, HIV infection, cancers, and neurodegenerative disorders*
- Identification de marqueurs de susceptibilité génétique à l'infection VIH, à l'athérosclérose, aux cancers et à la dégénérescence maculaire liée à l'âge / *Identification of genetic susceptibility markers for atherosclerosis, HIV infection, cancers, and neurodegenerative disorders.*

- Développement d'antagonistes des RCK CCR2 et CX3CR1 / *Development of CCR2 et CX3CR1 RCK antagonists*

Domaines d'applications / Fields of application

Maladies Infectieuses, maladies Inflammatoires, Maladies cardiovasculaires, maladies neurodégénératives, cancers / *Infectious diseases, Inflammatory diseases, cardiovascular diseases, neurodegenerative diseases, cancers*

Contrats de recherche récents / External peer-reviewed funding

- *Académique :*
 - ANR PIRIBIO (2009-2013), CHARMD (2009-2012), Parkemos (2010-2013), Chemokpain (2012-2016), Ickaire (2013-2015)
 - FP7 Endostem (2010-2015), RAID (2013-2016)
 - AFM Chemyo (2011-2014)
 - Emergence UPMC (2011-2013)
 - PHRC Solitox (2014-2016)
- *Industriel*
 - Roche, Solvay

Evaluateur de projets et membre de comités d'évaluation / Grant reviewer and member of grant review committees (récent)

ANR (The French National Research Agency - <http://www.agence-nationale-recherche.fr/>,

Membre de comités scientifiques / Member of scientific committee

- 2008-2012 CNRS Membre de la Commission Scientifique Spécialisée CSS24 " Interactions cellulaires" / *Member of the CNRS committee 24 "Cellular Interactions"*
- 2007- Inserm Membre de la commission de recherche clinique de l'Inserm (Avenir, Accueil,.. ;) / *Member of the Inserm clinical research committee (Young investigator, Md fellowship)*

Brevets et Demandes de brevet / Patents and patent applications

- Application No PCT/FR2008/052350 (filed December 17th, 2008) Modulators of the CX3CR1 receptor and therapeutic uses thereof. Co-inventors: K. Dorgham, P. Deterre, G. Gorochov and C. Combadiere.
- Application No EP11305816 (filed June 17th, 2011) ECL-1, un oligopeptide antagoniste de CCR2 et ses utilisations thérapeutiques. Co-inventors: C. Auvynet, F. Sennlaub, S. Chemtob, C. Quiniou and C. Combadiere.
- U.S. Patent No. 8,198,042 (filed 12/06/2012) « CC chemokine receptor 5 DNA, new animal models and therapeutic agents for HIV application » Co-inventors: C Combadiere and PM. Murphy.

Enseignement / Teaching

Encadrement / Supervision

▪ *Master and PhD programs*

| | | |
|---------------------------|---------------|---|
| En cours / <i>Current</i> | <u>PhDs</u> | B. G. Chousterman V. Felouzis P.L Lhoyer E. Aleman Navarro (Mex) |
| | <u>Master</u> | A. Coens, P. Hamon, M. Rahhab |

Anterieurs / Completed PhDs : S. Faure, A. Garin, E. Lavergne, M. Daoudi, C. Lécureuil, M. Rodero, K. Darbandi-Tehrani, J.E. Guet, A. Ghadiri, L. Poupel, S. Jacquelin, S. Rivas-Fuentes (Mex), T. Lopez (Mex), H. Chelbi (Tun), V. Ramos (Arg)

▪ **Postgraduate education medical doctors and postdocs**

En cours / Current L. Arnold, M. Rodero, C. Auvynet

Anterieurs / Completed A. Ghadiri, M. Otsuni,

Autres activités / Other activities

- Expert for the « Assistance Public-Hopitaux de Paris », contrat Interface 2004-2009 and 2010-2013.
- Participation to a program of prisoner rehabilitation.

Communication Grand Public / Outreach activities

Récentes participations à des évènements de vulgarisation scientifique

2009 : “Chercheurs en science, chercheurs de sens” (Pierre Valiron, Philippe Deterre, Editions de l’Atelier, 2009, Paris) co-authored with Pierre Valiron, astrophysicist, CNRS, Grenoble.

- Intervention dans des lycées et collèges
- Rencontres Internationales de la Recherche 2013, Le Louvre, Paris, France

Publications

Publications les plus représentatives / Selected publications

- Sennlaub F., Auvynet C., Calippe B., Hu S.H., Lavalette S., Dominguez E., Camelo S. Poupel L., Levy O., Guyon E., Saederup N., Charo I.F., Van Rooijen N., Nandrot E., Bourges J.-L., Behar-Cohen F., Sahel J.-A., Guillonnet X., Raoul W. and **Combadière C.** CCR2+ monocytes infiltrate atrophic lesions in age-related macular disease and mediate photoreceptor degeneration in a model of experimental subretinal inflammation. *EMBO Mol. Med.* 2013 Nov;5(11):1775-93.
- Jacquelin S., Licata F., Dorgham K., Hermand P., Poupel L., Guyon E., Deterre P., Hume D., **Combadière C.** and Boissonnas A. CX3CR1 reduces Ly6Chigh-monocyte motility within, and release from the bone marrow after chemotherapy in mice. *Blood* 2013 Aug 1;122(5):674-83.
- Darbandi-Tehrani K, Hermand P, Carvalho S, Dorgham K, Couvineau A, Lacapère JJ, **Combadière C** and Deterre P. Subtle conformational changes between CX3CR1 genetic variants as revealed by Resonance Energy Transfer assays. *FASEB J.* 2010, 24(11):4585-98.
- Boissonnas, A., A. Scholer-Dahirel, V. Simon-Blancal, L. Pace, F. Valet, A. Kissenpfennig, T. Sparwasser, B. Malissen, L. Fetler, and S. Amigorena. Foxp3+ T cells induce perforin-dependent dendritic cell death in tumor-draining lymph nodes. *Immunity.* 2010. 32:266-278.
- Dorgham K, Ghadiri A, Hermand P, Rodero M, Poupel L, Iga M, Hartley O, Gorochov G, **Combadière C** and Deterre P. An engineered CX3CR1 antagonist endowed with anti-inflammatory activity. *J Leukoc Biol.* 2009 Oct;86(4):903-11.
- Rodero M., Marie Y., Coudert M., Blondet E., Mokhtari K., Rousseaux A., Raoul W., Carpentier C., Sennlaub F., Deterre P., Delattre J.-Y., Debré P., Sanson M. and **Combadière C.** A polymorphism in the microglial cell mobilizing CX3CR1 gene is associated with survival in patients with glioblastoma. *J. Clin. Oncol.* 2008 Dec 20;26(36):5957-64.
- **Combadière C.**, Potteaux S, Rodero M, Simon T, Pezard A, Esposito B, Merval R, Proudfoot A, Tedgui A, Mallat Z. Combined inhibition of CCL2, CX3CR1 and CCR5 abrogates Ly-6C^{hi} and Ly-6C^{lo} monocytes and almost abolishes atherosclerosis in mice. *Circulation* 2008 Apr 1;117(13):1649-57.
- **Combadière C.**, Feumi C., Raoul W., Keller N., Rodéro M., Pezard A., Lavalette S., Houssier M., Jonet L., Picard E., Debré P., Sirinyan M., Deterre P., Ferroukhi T., Cohen S.-Y., Chauvaud D., Jeanny J.-C., Chemtob S., Behar-Cohen F. and Sennlaub F. CX3CR1-dependent subretinal

microglia cell accumulation is associated with cardinal features of age-related macular degeneration. **J. Clin. Invest.** 2007 Oct 1;117(10):2920-2928.

Publications 5 dernières années / Last 5 years

2013

- Sennlaub F., Auvynet C., Calippe B., Hu S.H., Lavalette S., Dominguez E., Camelo S. Poupel L., Levy O., Guyon E., Saederup N., Charo I.F., Van Rooijen N., Nandrot E., Bourges J.-L., Behar-Cohen F., Sahel J.-A., Guillonneau X., Raoul W. and Combadiere C. CCR2+ monocytes infiltrate atrophic lesions in age-related macular disease and mediate photoreceptor degeneration in a model of experimental subretinal inflammation. **EMBO Mol.Med** 2013 Nov;5(11):1775-93.
- Poupel L., Boissonnas A., Hermand P., Dorgham K., Guyon E., Auvynet C., Saint Charles F., Lesnik P., Deterre P. and **Combadiere C.** Pharmacological inhibition of the chemokine receptor CX3CR1 reduces atherosclerosis in mice. **Arterioscler.Thromb. Vasc. Biol.** 2013. Oct;33(10):2297-305. Jacquelin S., Licata F., Dorgham K., Hermand P., Poupel L., Guyon E., Deterre P., Hume D., **Combadiere C.** and Boissonnas A. CX3CR1 reduces Ly6Chigh-monocyte motility within, and release from the bone marrow after chemotherapy in mice. **Blood** 2013 Aug 1;122(5):674-83.
- Rodero M.P., Auvynet C., Poupel L., Combadiere B. and **Combadiere C.** Control of both myeloid cell infiltration and angiogenesis by CCR1 promotes liver cancer metastasis development in mice. **Neoplasia** 2013 Jun;15(6):641-8.
- Khan Z., **Combadiere C.**, Authier F.-J., Itier V., Lux F., Exley C., Mahrouf-Yorgov M., Decrouy X., Moretto P., Tillement O., Gherardi R.K. and Cadusseau J. Slow CCL2-dependent translocation of biopersistent particles from muscle to brain. **BMC Medicine** 2013 Apr 4;11:99.
- Boissonnas A., Licata F., Poupel L., Jacquelin S., Fetler L., Krumeich S., Théry C., Amigorena S. and **Combadiere C.** CD8+ Tumor-Infiltrating T cells are trapped in Tumor-Dendritic Cell Network. **Neoplasia** 2013 Jan;15(1):85-94
- Rodero M., Hodgson s., Hollier B., **Combadiere C.** and Khosrotehrani K. Reduced Il17a expression distinguishes a Ly6clow MHCIIhi macrophage population promoting wound healing. **J. Invest. Dermatol.** 2013 Mar;133(3):783-92.

2012

- Duffy D., Perrin H., Abadie V., Benhabiles N., Boissonnas A., Liard C., Descours B., Reboulleau D., Bonduelle O., Verrier B., Van Rooijen N., **Combadiere C.** and Combadiere B. Neutrophils Transport Antigen from the Dermis to the Bone Marrow, Initiating a Source of Memory CD8(+) T Cells. **Immunity** 2012 Nov 16;37(5):917-29.
- Cochain C., Auvynet C, Poupel L., Vilar J., Dumeau E., Richart A., Récalde A., Zouggar Y., HoWang K.Y., Bruneval P., Renault G., Marchiol C., Bonnin P., Lévy1 B., Bonecchi R., Locati M., **Combadiere C.**# and Silvestre J.-S.#. The chemokine decoy receptor D6 prevents excessive inflammation and adverse ventricular remodeling after myocardial infarction. **Arterioscler. Thromb. Vasc. Biol.** 2012 Sep;32(9):2206-13. #contributed equally to this work.
- Schulthess J., Meresse B., Ramiro-Puig E., Montcuquet N., Darche S., Bègue B., Ruummele F., **Combadiere C.**, Di Santo J.P., Buzoni-Gatel D. and Cerf-Bensussan N. IL-15-dependent NKp46+ innate lymphoid cells control intestinal inflammation via CCL3-CCR1-dependent recruitment of inflammatory monocytes. **Immunity** 2012 Jul 27;37(1):108-21.
- Raoul W., Poupel L., Tregouet D.-A., Lavalette S., Camelo S., Keller N., Krumeich S., Calippe B., Guillonneau X., Behar-Cohen F., Cohen S.-Y., Baatz H., **Combadiere C.**, Théry C., and Sennlaub F. MFGE8 does not influence chorio-retinal homeostasis or choroidal neovascularization in vivo. **PLoS One.** 2012;7(3):e33244.
- Bonduelle O., Duffy D., Verrier B., **Combadiere C.** and Combadiere B. Protective Effect of CX3CR1+ Dendritic Cells in a Vaccinia Virus Pulmonary Infection Model. **J. Immunol.** 2012 Feb 1;188(3):952-6.
- Ramos MV, Auvynet C., Poupel L., Rodero M., Mejias MP, Panek CA., Vanzulli S., **Combadiere C.**# and Palermo M.#. Chemokine receptor CCR1 disruption limits renal damage in a murine model of hemolytic uremic syndrome. **Am. J. Pathol.** 2012 Mar;180(3):1040-8. #contributed equally to this work

- Godefroy D., Gosselin R.-D., Yasutake A., Fujimura M., **Combadiere C.**, Maury-Brachet R., Laclau M., Rakwal R., Melik-Parsadaniantz S., Bourdineaud J-P and Rostène W. The chemokine CCL2 protects against methylmercury neurotoxicity. *Toxicol. Sciences*. 2012 Jan;125(1):209-18.

2011

- Gaudin F., Nasreddine S., Donnadiou A-C., Emilie D., **Combadiere C.**, Prévot S., Machelon V. and Balabanian K. Identification of the chemokine CX3CL1 as a new regulator of malignant cell proliferation in epithelial ovarian cancer. *Plos One* 2011;6(7):e21546
- Lavalette S, Raoul W, Houssier M, Camelo S, Levy O, Calippe B, Jonet L, Behar-Cohen F, Chemtob S, Guillonneau X, **Combadière C** and Sennlaub F. Interleukin-1 β inhibition prevents choroidal neovascularization and does not exacerbate photoreceptor degeneration. *Am J Pathol*. 2011 May;178(5):2416-23.

2010

- Darbandi-Tehrani K, Hermand P, Carvalho S, Dorgham K, Couvineau A, Lacapère JJ, **Combadière C** and Deterre P. Subtle conformational changes between CX3CR1 genetic variants as revealed by Resonance Energy Transfer assays. *FASEB J*. 2010, 24(11):4585-98.
- Cochain C., Rodero M., Vilar J., Récalde A., Richart A., Loinard C., Combadiere B., Poupel P., Zouggar Y., Duriez M., Lévy B.I., Mallat Z., **Combadiere C.** and Silvestre J-S. Regulation of monocyte subsets systemic levels by distinct chemokine receptors controls postischemic neovascularization. *CardioVasc. Res*. 2010 88(1):186-95.
- Wang Y, Ait-Oufella H, Herbin O, Bonnin P, Ramkhalawon B, Taleb S, Huang J, Offenstadt G, **Combadière C**, Rénia L, Johnson JL, Tharaux PL, Tedgui A, Mallat Z. TGF-beta activity protects against inflammatory aortic aneurysm progression and complications in angiotensin II-infused mice. *J Clin Invest*. 2010 Feb 1;120(2):422-32.
- Martino A, Badell E, Abadie V, Balloy V, Chignard M, Mistou MY, Combadière B, **Combadière C**, Winter N. Mycobacterium bovis Bacillus Calmette-Guerin Vaccination Mobilizes Innate Myeloid-Derived Suppressor Cells Restraining In Vivo T Cell Priming Via IL-1R-Dependent Nitric Oxide Production. *J Immunol*. 2010 Feb 15;184(4):2038-47
- Conforti R, Ma Y, Morel Y, Patrel C, Terme M, Viaud S, Ryffel B, Ferrantini M, Uppaluri R, Schreiber R, **Combadière C**, Chaput N, André F, Kroemer G, Zitvogel L. Opposing effects of toll-like receptor (TLR3) signaling in tumors can be therapeutically uncoupled to optimize the anticancer efficacy of TLR3 ligands. *Cancer Res*. 2010 Jan 15;70(2):490-500.

2009

- Dorgham K, Ghadiri A, Hermand P, Rodero M, Poupel L, Iga M, Hartley O, Gorochov G, **Combadière C** and Deterre P. An engineered CX3CR1 antagonist endowed with anti-inflammatory activity. *J Leukoc Biol*. 2009 Oct;86(4):903-11.
- Franciszkievicz K, Le Floch A, Jalil A, Vigant F, Robert T, Vergnon I, Mackiewicz A, Benihoud K, Validire P, Chouaib S, **Combadière C**, Mami-Chouaib F. Intratumoral induction of CD103 triggers tumor-specific CTL function and CCR5-dependent T-cell retention. *Cancer Res*. 2009 Aug 1;69(15):6249-55.
- Baatz H, Poupel L, Coudert M, Sennlaub F and **Combadiere C**. Polymorphisms of Complement Factor Genes and Age-Related Macular Degeneration in a German Population. *Klin Monatsbl Augenheilkd*. 2009 Apr 27.

Reviews and book Chapters

- Bachelier F., Ben-Baruch A., Burkhardt A.M., **Combadiere C.**, Farber J.M., Graham G.J., Horuk R., Sparre-Ulrich A.H., Locati M., Luster A.D., Mantovani A., Matsushima K., Murphy P.M., Nibbs R, Nomiya H., Power C.A., Proudfoot A.E.I., Rosenkilde M.M., Rot A., Sozzani S., Thelen M., Yoshie A. and Zlotnik A. International Union of Pharmacology LXXXIX Update on the Extended Family of Chemokine Receptors And Introducing a New Nomenclature for Atypical Chemokine Receptors. *Pharmacol. Rev.* 2013 Nov 11;66(1):1-79.

- **Combadiere C.**, Raoul W., Guillonneau X. and Sennlaub F. Comment on "Ccl2, Cx3cr1 and Ccl2/Cx3cr1 chemokine deficiencies are not sufficient to cause age-related retinal degeneration" by Luhmann et al. *Exp Eye Res.* 2012 Dec 8. *Exp Eye Res.* 2013 Feb 9.
- Franciszkiewicz K., Boissonnas A., Boutet M., **Combadiere C.** and Mami-Chouaib F. Role of chemokines and chemokine receptors in shaping the effector phase of the antitumor immune response. *Cancer Res.* 2012 Dec 7
- Gergnon J and **Combadiere C.** Role of Chemokines Polymorphisms in Diseases. *Immunol Lett.* 2012 Jul 30;145(1-2):15-22.
- Raoul W, **Combadière C**, Sennlaub F. Les chimiokines et leurs récepteurs, Nouvelles cibles thérapeutique. *Basse Vision Infos* 2011 sept; Review. French
- Raoul W, Auvynet C, Camelo S, Guillonneau X, Feumi C, **Combadière C**, Sennlaub F. CCL2/CCR2 and CX3CL1/CX3CR1 chemokine axes and their possible involvement in age-related macular degeneration. *J Neuroinflammation.* 2010 Dec 2;7:87.
- Atherosclerosis : on the trail of chemokines. Poupel L and **Combadiere C.** *Biol Aujourdhui.* 2010;204(4):285-293.
- Role of chemokines in the development of age-related macular degeneration. Raoul W, Lelièvre E, Auvynet C, Feumi C, **Combadière C** and Sennlaub F. *Biol Aujourdhui.* 2010;204(4):311-319.