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QUESTION D'ACTUALITÉ/TOPICAL QUESTION

Faecal microbiota transplantation: A *sui generis* biological drug, not a tissue

Transplantation de microbiote intestinal : un médicament biologique *sui generis*

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Summary Responding to Smith et al. (Nature, 2014), this paper argues that for medical use, faecal microbiota transplantation (FMT) should be considered a *sui generis* biological drug, rather than a tissue. Smith and colleagues' thesis is based on possible undesirable economic consequences of this designation — not on its scientific and conceptual basis. The faecal transplant (including gut microbiota, metabolites, mucus, human cells, viruses, fungi, etc.) is not a tissue; it is of topographic — not cellular — human origin. We consider the donor a bioreactor, producing the faecal substrate of therapeutic interest. The debate is of singular importance as the FDA considers FMT a drug and released a new guidance for public consultation in February 2014, whereas to date the European Medicines Agency has not promulgated its position. The UK's National Institute for Heath and Care Excellence does not consider FMT to involve the

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transplantation of body tissue, and in March 2014 the French regulatory agency ANSM expressly declared it to be a drug. As FM is a complex and highly variable admixture, its components cannot be completely characterized, and to date, compositional quality cannot be assessed. We consider FMT to be a *sui generis* biologic drug, albeit one prepared with unconventional raw material under microbiologic control. The possibility of associating identified bacterial species with particular diseases and cultivating selected bacteria of therapeutic interest would certainly define a second generation of microbiome therapeutics, but is still speculative.

MOTS CLÉS
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Résumé Le transfert de microbiote intestinal relève de la qualification de médicament biologique *sui generis*, non de la qualification de transplantation de tissus comme le soutiennent Smith et al. (Nature, 2014). La thèse de Smith et al. est basée sur les conséquences économiques indésirables des qualifications, non sur leur fondement scientifique et conceptuel. La FDA considère cette pratique comme un médicament expérimental, l'ANSM comme un médicament dans une indication unique, le NICE considère qu'il ne s'agit pas d'une transplantation, et l'EMA n'a pas encore pris position à la date de cet article. L'*inoculum* (incluant microbiote, metabolites, cellules humaines, mucus, champignons, virus) est d'origine humaine au sens topographique et non cellulaire. Nous considérons le donneur comme un bioréacteur qui produit le substrat fécal d'intérêt thérapeutique, une composition complexe et hautement variable. L'impossibilité d'en caractériser les substances et de déterminer sa qualité nous conduit à considérer qu'il s'agit d'un médicament biologique *sui generis*, préparé avec une matière première non conventionnelle sous contrôle microbiologique. Si l'on parvenait à associer des espèces bactériennes à la guérison d'une maladie, à les cultiver et les utiliser de façon sélective, une nouvelle génération de thérapies permettant la modulation du microbiome humain apparaîtrait. Mais cette hypothèse est encore spéculative.

Faecal Microbiota Transplant or Transfer (FMT) is a mechanism for restoring the human physiological balance by transferring gut microbiota from a healthy donor. This technique is of immediate interest in the treatment of severe recurrent *Clostridium difficile* infection [1] and of promising — but still speculative — interest for other disorders (inflammatory bowel disease, irritable bowel syndrome, metabolic syndrome, etc. associated with microbial dysbiosis), whose aetiologies are unknown or uncertain [2]. FMT appears to be a plausible alternative to ineffective, unavailable or potentially harmful chemical or biological therapies.

Smith and colleagues argue that for medical use, human stool should be considered a tissue — not a drug [3]. In their paper they emphasize that for FMT to be regulated as a drug would be overly restrictive, requiring physicians to submit time-consuming Investigational New Drug applications before performing FMT. Such burdensome rules might encourage people to seek treatment outside the conventional medical establishment, and for some even to seek to use their pets as donors. Restrictive rules would also disrupt the fecund research and business ecosystem that has grown up in the current, relatively unrestricted climate, by confining FMT to companies with the resources to fund large clinical trials. It would also threaten the development of research and stool banks supported by for-profit and non-profit organizations alike.

These arguments are based on the possible undesirable economic consequences of regulating FMT as a drug — not on its scientific and conceptual basis. The debate is of singular importance, as the FDA considers FMT to be a drug and released a new guidance for public consultation in February 2014 [4]. By contrast, the European Medicines Agency has not yet promulgates its position. The UK's National Institute or Health and Care Excellence (NICE) has stated that it does not consider FMT to involve the transplantation of body tissue, [5] and in March 2014 the French regulatory agency ANSM expressly declared it to be a drug [6]. Defining the status for FMT is clearly a challenging regulatory issue. Classical definitions are of limited value — as neither human-originated 'tissue' nor 'conventional drug' seem relevant classifications for a therapy intended for microbiome modulation.

The aim of gut microbiota transfer (referred to by Smith and colleagues as faecal transplant) is to restore a broken dialogue between human cells and the bacteria hosted in the gut. The contribution of this symbiosis to human physiological balance has been well known (albeit not classified or controlled) for centuries [7]. The progressive understanding and possible modulation of the microbiome has suggested a range of therapeutic applications, stimulated global scientific networking, and raised huge funding [8,9].

The importance of gut microbiota and its symbiotic interactions within the human body justify its designation as a ''super-organism'' [10] or integrated metabolic space [11]. Some authors consider it to be a ''virtual organ'' [12] while others claim ''we are what we host'' [13] — and the as-yet unexplored importance of the human cell-bacteria symbiosis could give truth to this. However, these

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