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COMMENTARY

The Unique Potential for Noninvasive Imaging in Modernizing Drug Development and in Transforming Therapeutics: PET/MRI/MRS

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The classical principles of effective pharmacotherapy requires that the patient to be treated receive the right drug, at the right rate, at the right dose, and at the right site. Knowing what is "right" requires our ability to measure the PK/PD of drugs at their target site(s), and that is now possible using those noninvasive imaging methods that allow for molecular imaging—nuclear imaging and magnetic resonance spectroscopy (MRS[1]). Within nuclear imaging, PET (positron emission tomography) using drugs radiolabeled with ^{11}C and ^{18}F is the technique of choice for PK/PD studies, whereas the nuclides most suitable for PK/PD studies using MRS are ^{1}H, ^{13}C, ^{19}F and ^{31}P.

While these noninvasive imaging techniques have and are providing unique information on drug biodistribution, targeting, metabolism and PK/PD, they also have a number of significant limitations. Nuclear/PET imaging, albeit a very highly sensitive technique, does not provide information about what chemical entities are being measured—all compounds containing the radioactive atom will contribute to the signal. MRS, on the other hand, has much lower sensitivity, and signals from atoms that are held rigidly in the x, y or z planes may be broadened to the point where they are not detectable. However, even with such limitations, both nuclear/PET and MRS by themselves are tremendously useful in drug studies in animals and humans.

There is one development that can change this picture in a major and significant manner: the development of a single combined instrument which can perform simultaneously PET and MRI/MRS measurements (1–3). This paper will discuss what is unique and different in PET/MRI/MRS measurements as opposed to similar measurements performed separately rather than simultaneously.

A living organism is by definition a dynamic system, regulated by a series of biochemical, physiological, and, in the case of patients, pharmacological processes. Thus, an individual at time T(1) may be very similar to that same individual at time T(2), but will never be identical, and thus a direct correlation between data acquired at time T(1) and T(2) may or may not be possible. This may be of special concern in drug studies when there is a significant temporal difference, as there would be in measurements using PET and those using MRI/MRS. In another vein, SPECT/MRI is another dual technique that is especially useful in the noninvasive quantitative and kinetic measurements of receptors (4).

Table 1 illustrates the advantages and limitations of these three approaches: PET, MRI/MRS and combined PET/MRI/MRS

Let us now apply these principles to drug studies. The pharmacological information we need to know, first during the process of drug development and, subsequently, when that drug is being used clinically for therapeutics decisions, includes knowing 1) the right drug for a specific patient, 2) the right dose needed to obtain the best response, 3) the right rate at which this drug needs to be given to obtain the best response (pharmacokinetic optimization), and 4) the right site (target) where this drug needs to be delivered.

The current paradigm is that the above answers are obtained through clinical trials, which define the probabil-

[1] While in the physical sciences, such as in chemistry, the proper term is nuclear magnetic resonance spectroscopy, NMR for short, the medical sciences have dropped the word "nuclear," and the terms used are MRI for Magnetic Resonance Imaging and MRS for Magnetic Resonance Spectroscopy.

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Table I Comparison of the Various Noninvasive Imaging Methods: Advantages, Limitations and What Can Be Measured

	Advantages	Limitations	Information that is generated
PET (and PET-CT)	Quantitative data Highest sensitivity of detection	Lack of chemical (metabolic) information—the measure is the sum of all radiolabeled agents and metabolites	Biodistribution and targeting of drugs and metabolites following administration of radiolabeled agents
MRI	Images soft tissues and good anatomical registration; delivers no ionizing radiation	Claustrophobia	Anatomical and functional information; limited perfusion and PK/PD information
MRS	Allows noninvasive chemical analysis of multiple molecular products	Low sensitivity of detection Only a limited number of compounds can be measured	Drugs and their metabolites can be measured *in vivo* and noninvasively
Combined PET/MRI	Allows for both anatomical and functional information without additional ionizing radiation	In addition to the above, requires a highly specialized instrument, still in development	The ability to provide, in one single setting, simultaneous anatomical, functional and dynamic information
Combined SPECT/MRI	Allows for both anatomical and some functional information	Of limited use with radiolabeled drugs; used mostly with drug analogs	Easier to use in many instances than PET; especially useful with ^{99m}Tc and ^{123}I
Combined PET/MRI/MRS	Combines all the advantages: anatomy, functional, biodistribution and site-specific metabolism	As is the case for PET/MRI, requires a highly specialized instrument, still in development	The ability to provide, in one single setting, simultaneous anatomical, functional, dynamic and pharmacokinetic information

ities of response of groups of patients with specific characteristics. Recent advances in pharmacogenomics have done much to narrow the focus to groups of patients having specific genomic characteristics (presence or absence of a specific or a series of genes), but they still lack information on the phenotype of a specific patient. While drug levels can be readily monitored in blood, saliva, and excreta, measuring drug levels in tissues requires biopsy specimens, which will only be available under extremely special conditions. Such measurements appear to be highly suitable for infectious and other diseases where blood levels are rate determining; they are not sufficient in the treatment of oncological, neurological and other diseases where tissue levels are rate-determining.

We postulate that an integrated PET/MRI/MRS system can provide, in one single setting, simultaneous anatomical, functional, dynamic, and pharmacokinetic information, and we wish to illustrate that with a specific example that makes use of the unique potential of fluorinated drugs, which can be studied using ^{18}F, a positron emitter with a half-life of 2 h, and for the magnetic resonance spectroscopy studies, using ^{19}F. Natural fluorine is monoatomic (100% ^{19}F); hence, fluorinated drugs require no isotope enrichment. ^{19}F has the highest NMR sensitivity (84%) next to ^{1}H, and because there are no naturally occurring fluorinated compounds, ^{19}F NMR signals will only be observable from the drugs being administered for such a study. However, while the ^{18}F/^{19}F pair is a superb model for PET/MRS studies, such studies can then be generalized to most other drugs using e.g. ^{11}C for PET radiolabeling, and either ^{13}C or ^{1}H for the MRS studies.

There is another caveat that needs to be considered. In addition to being possible, expensive imaging studies also need to meet a clear clinical and societal need. The pharmacologically oriented studies uniquely possible using PET/MRI/MRS will also have to be evaluated whether this new technology also meets the criteria of desirability and cost-effectiveness, recently discussed in a Perspective paper by Hillman and Goldsmith (5). Like all new methodologies, this will have to be proven.

Let us now illustrate the unique potential of PET/MRI/MRS with 5-Fluorouracil, an anticancer drug that has been in clinical use since the late 1950s. While it is viewed as an "old" drug, it continues being used in a very active manner as part of the treatment of many solid tumors (6–8). My laboratory has performed for years nuclear imaging with ^{18}F-5FU and, subsequently, ^{19}F-MRS studies with that drug (9–12). The unique advantages of both ^{18}F for PET and ^{19}F for MRS have been presented above.

The metabolism of 5-Fluorouracil gives rise to a number of compounds, all of them fluorinated. Hence, when images are obtained after administration of ^{18}F-5FU (13), the ^{18}F-image obtained reveals the sum of all the fluorinated compounds at each tissue site, with no chemical differentiation between active and inactive compounds. When ^{19}F-spectra are obtained following administration of 5-FU, peaks representing 5-FU and the main catabolite (FBAL) can be readily observed in both animal (14) and human studies (15), and in many cases, a peak is the sum of the free fluoro-nucleosides/nucleotides (FNUC).

Full pharmacokinetic modeling of such a system might be possible by assuming a compartment in every tissue and organ for each compound in Fig. 1, but such a very large and complex compartmental would neither be analyzable nor really provide meaningful information. A possible simplified model is illustrated in Fig. 2.

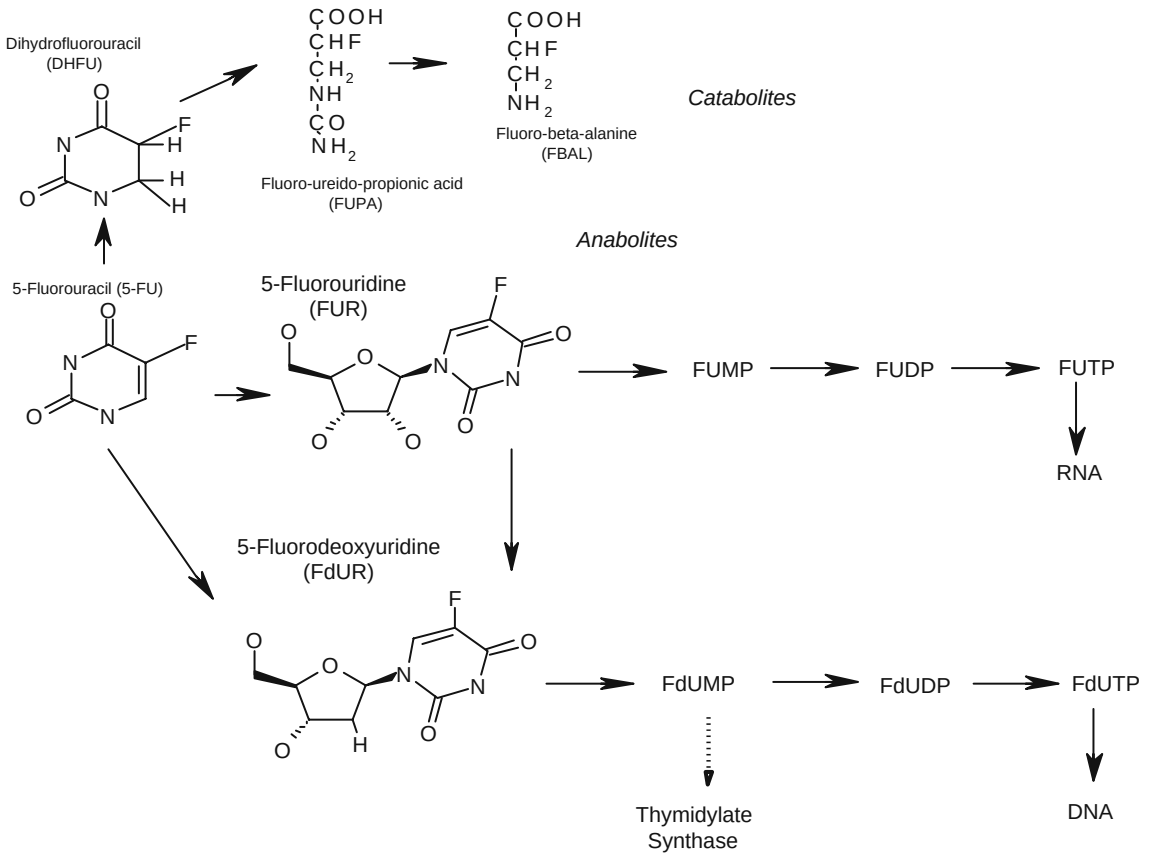

Fig. 1 Metabolism of 5-Fluorouracil

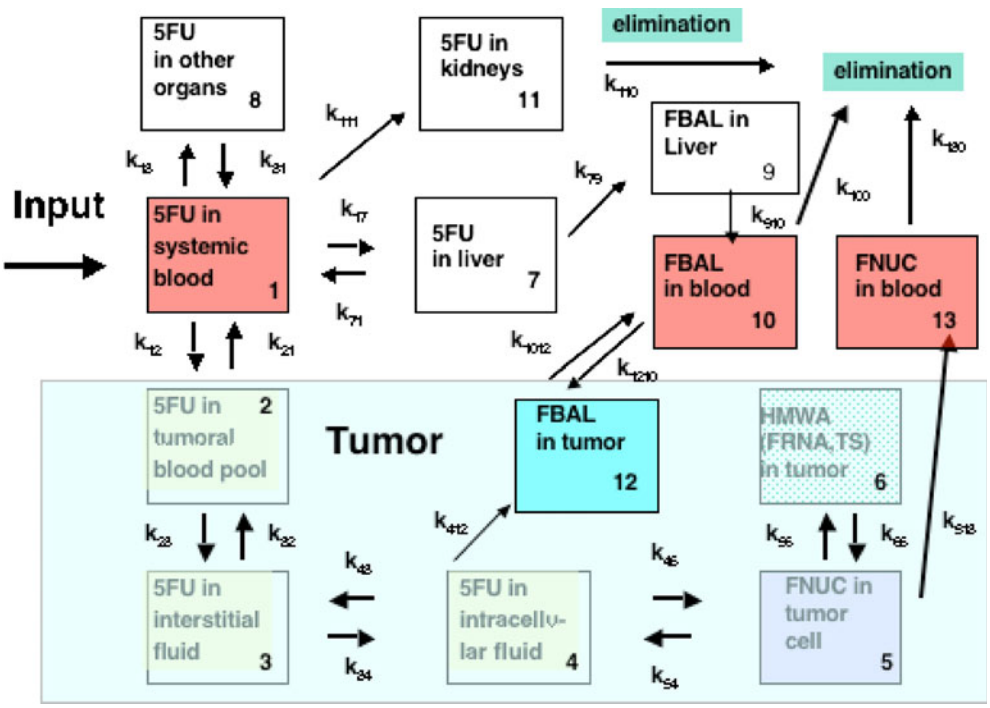

Fig. 2 Compartmentalized flow chart of 5-Fluorouracil -13 compartments and 24 rate constants

Focusing on the tumor, what PET will measure is a sum of all four products in six compartments, and what ^{19}F-MRS will measure is the sum of free 5-FU in compartments 2, 3 and 4, the free FBAL and the free FNUCs (the sum of fluoronucleotides/fluoronucleosides, lumped together in in vivo imaging). By difference, it allows the estimation of the ultimately active species in compartment 6—fluorinated RNA, fluorinated DNA, and the ternary 5-FU-thymidilate synthase complex. ^{18}F-PET and ^{19}F-MRS of the liver will allow for quantitation of free 5-FU and its catabolites, and these same techniques as well as conventional laboratory measurements will allow identification and quantitation of 5-FU, catabolites and anabolites in blood.

The information generated by such a study may provide answers to the four key pharmacological questions raised above: whether this agent (5FU in this model example) is the right drug to be used or not, whether the dose administered is in a range to generate an optimal level of active anabolite at the tumor site, and whether the rate and the site at which this drug is administered optimize the competing kinetics of delivery, elimination and metabolism.

What is the advantage, and perhaps the necessity, of performing PET and MRS studies simultaneously, rather than consecutively? Simultaneous measurements ensure that data are acquired from the same individual—physiologically, pharmacologically, functionally. Consecutive measurements, separated by hours or days, are likely to introduce variabilities that may prevent the two sets of data from being used concurrently. Again, and like in all new methodologies, this will have to be proven.

In conclusion, understanding the fate of drugs in living systems requires an understanding of their pharmacokinetics and their pharmacodynamic effects at target sites. Developing full physiologically based pharmacokinetic (PBPK) models may now be possible inasmuch as we can generate simultaneously anatomical, functional and PK/PD information from target organ and tissues using noninvasive imaging. In such an integrated approach, PET imaging using ^{18}F or ^{11}C allows for high sensitivity and high temporal resolution, and MRS, using ^{19}F, ^{13}C or ^{1}H, allows for high chemical information. Integrating both technologies with a concurrent knowledge of the pharmacogenomics of that patient will allow for a true systems approach to key drug studies in humans for effective personalized/individualized treatment. It may thereby aid in selecting as quickly as possible the most viable drugs candidates out from the large pool of drug candidates available

REFERENCES

1. Catana C, Wu Y, Judenhofer MS, Qi J, Pichler BJ, Cherry SR. Simultaneous acquisition of multislice PET and MR Images: initial results with a MR-compatible PET scanner. J Nucl Med. 2006;47:1968–76.
2. Judenhofer MS, Wehrl HF, Newport DF, Catana C, Siegel SB, Becker M, *et al.* Simultaneous PET-MRI: a new approach for functional and morphological imaging. Nat Med. 2008;14:459–65.
3. Pichler BJ, Kolb A, Nägele T, Schlemmer H-P. PET/MRI: Paving the Way for the Next Generation of Clinical Multimodality Imaging Applications. J Nucl Med. 2010;51:333–6.
4. Peremans K, De Spiegeleer B, Buntinx E, Dobbeleir A, Vermeire S, Vandermeulen E, *et al.* Evaluation of serotonin-2A receptor occupancy with 123I-5-I-R91150 and single-photon emission tomography before and after low-dose pipamperone administration in the canine brain. Nucl Med Commun. 2008;29:724–9.
5. Hillman BJ, Goldsmith JC. The Uncritical Use of High-Tech Medical Imaging. N Engl J Med. 2010;363:4–6.
6. Heidelberger C, Chaudhuri NK, Danneberg P, Mooren D, Griesbach L, Duschinsky R, *et al.* Fluorinated Pyrimidines, A New Class of Tumour-Inhibitory Compounds. Nature. 1957;179:663–6.
7. Pinedo HM, Peters GF. Fluorouracil: biochemistry and pharmacology. J Clin Oncol. 1988;6:1653–64.
8. Rustum YM. Fluoropyrimidines in Cancer Therapy. Totowa: Humana Press; 2003.
9. Shani J, Wolf W. A Model of Prediction of Chemotherapy Response to 5-FU in Sensitive versus Resistant Lymphocytic Leukemia in Mice. Cancer Res. 1977;37:2306–8.
10. Young D, Vine E, Ghanbarpour A, Shani J, Siemsen JK, Wolf W. Metabolic and Distribution Studies with Radiolabeled 5-Fluorouracil. Nucl Med. 1982;21:1–7.
11. Wolf W, Presant CA, Servis KL, El-Tahtawy A, Albright MJ, Barker PB, *et al.* Tumor Trapping of 5-Fluorouracil: in vivo 19F - NMR Spectroscopic Pharmacokinetics in Tumor-bearing Humans and rabbits. Proc Natl Acad Sci. 1990;87:492–6.
12. Presant CA, Wolf W, Waluch V, Wiseman C, Kennedy P, Blayney D, *et al.* Association of the Intratumoral Pharmacokinetics of 5-Fluorouracil with Clinical Response: an In-Vivo 19F Nuclear Magnetic Resonance Study. Lancet. 1994;343:1184–7.
13. Wolf W, Presant CA, Waluch V. Noninvasive Studies of Fluoropyrimidines. In Fluoropyrimidines in Cancer Therapy. In: Youcef Rustum, editor. Cancer Drug Discovery and Development series. Totowa: Humana Press; 2003.
14. Stevens AN, Morris PG, Iles RA, Sheldon PW, Griffiths JR. 5-Fluorouracil metabolism monitored in vivo by of 5-FU catabolites in human liver. Br J Cancer. 1984;50:113–7.
15. Wolf W, Presant CA, Waluch V. 19F-MRS Studies of Fluorinated Drugs in Humans. Adv Drug Deliv Rev. 2000;41:5–74.