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Fluorescent Biosensors – Promises for Personalized Medicine

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Have you ever fantasized about the day when you would simply walk into the doctor's office, drink a cocktail of "diagnostic juice" and enter an infra-red chamber which would illuminate any signs of disease?

To most of us the perspective of diagnostics through molecular imaging is currently unimaginable and one might argue that we are far from witnessing such a dream come true, the technological improvements required and obstacles to overcome being far too great. Yet, the advances in fluorescence imaging technologies, together with the emergence of novel chemical probes, fluorescent biosensors and molecular tracers, and the development of new generations of nanocarriers that are particularly well suited for *in vivo* applications, are now providing a glimpse of hope.

Fluorescent biosensors consist of a peptide, protein or polymeric scaffold, which can recognize a biomolecular target or biomarker and report on this recognition event through changes in the fluorescent properties (wavelength, intensity, life-time) of the fluorescent probes which are genetically, chemically or enzymatically coupled to the scaffold. Fluorescent biosensors undoubtedly constitute one of the most promising classes of tools for detection of biomarkers *in vitro*, in cellulo and *in vivo*, for probing their relative abundance, their activity or their conformation, and for monitoring dynamic molecular events in real-time. The opportunities offered by these tools with respect to technological and medical innovation are countless. Fluorescent probes allow to visualize targets which cannot be detected by the human eye and which would normally require extraction of a biopsy for *ex vivo* detection of a biomarker by classical antigenic approaches. Hence, the development of imaging bioprobes for detection of disease biomarkers in pathological disorders such as cancer or viral infection, currently provides much excitement and expectation for early stage diagnostics, for monitoring response to therapeutics, and for image-guided surgery.

Unfortunately, the road leading to development of biosensors which stand a chance of success in biomedical imaging applications is mined with challenges and constraints. Recurrent issues include specificity (or lack) in complex samples, sensitivity and robustness of the fluorescent signal required for statistically significant detection of biomarkers in the context of a diagnostic approach, the signal to noise ratio which should allow to distinguish between healthy and diseased cells and tissues, the stability of the probe over time, and its bioavailability versus a lack of toxicity and immunogenicity. Moreover, a major obstacle for clinical application of fluorescent biosensors concerns gaining FDA approval for the fluorescent probe itself, whether conjugated to a carrier, tracer or biosensor. So far only IGC (indocyanine green) has passed the strict regulations underlying application of dyes for biomedical imaging in humans.

Ideally, in addition to being bright and photostable, fluorescent bioprobes should be cell permeant, non toxic, non-immunogenic, and perfectly well tolerated by the organism. In the real world it is practically impossible to meet all of these requirements/criteria in a single molecule. Hence, a major bottleneck for *in vivo* applications concerns the delivery of fluorescent biosensors into cells, tissues and organs. In practice, this involves engineering biosensor formulations with nanocarriers which are stable in bodily fluids, and which can be delivered to their target passively, through prolonged circulation and enhanced permeability retention in the tumour for instance, or actively, thanks to specific targeting sequences. Such multifunctional formulations must further allow the biosensor to recognize its target and respond appropriately. Associated with this issue are the questions of homogeneity of administration and of depth of tissue penetration.

Despite the challenges in designing efficient strategies for imaging biomarkers *in vivo*, several fluorescent probes are emerging as potent tools for biomedical applications. Near-infra-red probes that have been used for optical imaging for some time, such as ICG for visualizing angiogenic structures, have been coupled to carrier molecules, like albumin and used to highlight sentinel lymph nodes [1]. Moreover, near-infrared dyes have been targeted to specific cell-surface antigens and receptors, such as integrins and GLUT receptors, through conjugation with RGD and 2-deoxyglucose, respectively [2,3] to image tumours *in vivo*. Yet another successful example is the fluorescent peptide tracer that binds nerves selectively, thereby enabling direct visualization of peripheral nerves during surgery, and contributing to limit their damage during intervention [4]. Besides targeting strategies aimed at directing fluorescent tracers towards specific cell subtypes, "smart probes" have been developed which make use of properties inherent to cancer cells for penetration and activation. For instance metalloproteases secreted at the vicinity of tumours cleave target sequences which normally prevent the probe from penetrating cells in a non-specific fashion, thereby releasing a cell-penetrating sequence which allows for endosomal uptake of the probe [5-7]. Other systems are activated by the acidic pH that characterizes the tumour environment, such as pH-activatable fluorescent moieties coupled to cancer-targeting antibodies [8], and pH-activatable cell-penetrating peptides conjugated to a fluorescent probes (PHLIP technology) [9]. Yet another strategy consists in devising means of silencing a fluorescent probe through molecular quenching until specific enzymes release the molecular cage. This strategy has been applied to generate a fluorescent probe activated by tumour-specific gamma-glutamyl transferases (GGT) [10], which can be applied topically to probe fluorescence at local tumour sites, and which allows for rapid visualization of surface lesions upon intraoperative detection of tumours and metastases. Last but not least are the strategies which simply rely on detection of major differences in biomarker levels, such as the FRET biosensor developed for clinical diagnosis of Bcr-Abl kinase activity in chronic myeloid leukemia (CML), which can further be employed to assess drug efficacy as well as for HTS/HCS screening of novel inhibitors of this kinase [11,12].

Changes in society are closely associated with technological

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developments – medicine is currently witnessing significant changes thanks to major advances in nanotechnology and imaging technologies. Following the bench to bedside concept which has lead scientists to devise molecular therapies which are amenable to the patient, the emerging concept of individualized cancer therapy is now calling for development of methods for imaging disease biomarkers, monitoring individual health characteristics and assessing therapeutic response. Ongoing efforts in developing biosensor technologies suited for *in vivo* detection of biomarkers allow to contemplate the perspective of "illuminating nanomedicine" for early stage diagnostics, monitoring disease progression and response to therapeutics. This alone is a revolutionary step in healthcare. Remaining challenges include development of multiplex detection systems and multimodal approaches, which would facilitate combination diagnostics, reporting simultaneously on several disease biomarkers, and employing different technologies such as molecular imaging, positron emission tomography and/or magnetic resonance, to gain a broader spectrum of information. There is still a long way to personalized diagnostics and monitoring of therapeutic benefits. However it is clear that the combined strategies proposed by chemists, biologists and physicist to provide sensitive and non-invasive imaging tools for *in vivo* applications, are offering new opportunities to reach this goal. So the day when Dr. H. will ask us to step inside an infra-red chamber to diagnose our health status through "nanomedical illumination" may be much closer than we expect.

The publication of studies concerning design, engineering and optimization of fluorescent biosensors in an open access journal such as Journal of Biosensors and Bioelectronics is essential to validate and diffuse the potential of these tools beyond the scope of their individual thematic field. Indeed, whilst the development of genetically-encoded fluorescent biosensors may allow the biologist to probe his favourite enzyme within a specific physiological or pathological setting, readers will most certainly be brought to appreciate broader applications of this technology to the biomedical or drug discovery world. Likewise development of peptide-based fluorescent probes by chemists which have not yet been exploited to address biological questions in a living environment, become available to the eyes of biologists, who may suggest transversal technologies for application of these tools to living cells and animal models.

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