Protein Conjugation Serves Life Sciences Applications

Fleet Bioprocessing has developed a range of protein conjugation and purification techniques for use in the life sciences, and is establishing strategic alliances to enhance its technology offering.

Founded in 2000, UK company Fleet Bioprocessing offers a range of reagent development, validation and manufacturing services within the life science marketplace, with key expertise in protein conjugation and purification techniques.

The company originates from the clinical diagnostics sector, where optimisation of conjugation procedures has been recognised as a core technology since the earliest radiolabelling studies of the 1940s. Although when Fleet Bioprocessing was set up in 2000 it was primarily to service the diagnostics market, it soon became apparent to the company's management that its depth of conjugation knowledge could help fill some real skill gaps in the pharmaceuticals sector.

"Conjugated protein drugs have received an ever-increasing level of interest in the past few years, but so far there appears to have been little recognition within the pharma sector that there is a large body of knowledge 'out there' whose application could pay big dividends for drug developers," says managing director, Alastair Dent. "The capabilities offered by Fleet Bioprocessing are not based on a single technology – and indeed the company strongly believes that no 'one size fits all' approach can give the best performance in all circumstances. What it offers is in-depth knowledge of *all* the available conjugation technologies and techniques," he says.

Multiple advantages of conjugated biopharmaceuticals

The potential advantages offered by conjugated biopharmaceuticals as a category are manifold:

- the classic 'magic bullet' approach first advanced by Paul Ehrlich in about 1900 requires a single entity to combine the desired therapeutic properties with the ability to localise at the desired target. Examples where these two properties are found within a single protein molecule are very rare – but by coupling a (protein or non-protein) therapeutic entity to a targeting protein such as an antibody, this combination of properties can readily be achieved
- conjugation techniques such as PEGylation with polyethylene glycol have long been recognised as useful tools for modifying *in vivo* drug properties with respect to biotransport properties, clearance rates, and so on.
- the conjugation of multiple therapeutic protein 'copies' to a carrier backbone can offer the potential of significant amplification over the performance of a protein monomer.

"At a more detailed level, the impact that the exact nature of the conjugation chemistry can have on biopharmaceutical performance is not as clearly recognised within the sector as might be expected," says Dent. "Different coupling agents have different properties with respect to key pharmaceutical parameters such as immunogenicity and bioavailability of the conjugate components. Controllable variables such as reaction ratios and conditions and purification methods would be expected to have a significant impact too. There are many techniques available for the optimisation of conjugate performance to 'tune' conjugate performance, reasonably well-known in the diagnostics sector but considerably less so in the pharma field.

"Similarly, such factors can have a major impact on process yield and robustness – so the impact goes beyond drug performance *per se* to economic and manufacturability issues. Even during the development phase, factors such as efficient use of scarce protein resources can be an important time-to-market issue.

"Finally, the ability of a conjugate to be sufficiently characterisable to be acceptable to regulatory authorities is strongly dependent on the chemistry employed – another key factor in the route to market," he says.

Dent observes that given the lack of knowledge in this speciality within the pharmaceutical sector, it is undoubtedly the case that good drugs are 'sitting out there' undiscovered because insufficient effort has been applied to optimisation of conjugation procedures. "World-class diagnostic manufacturers do not expect to achieve exquisite assay sensitivity without putting the appropriate level of effort into conjugate optimisation – and the same principle applies, possibly even more strongly, to the development of marketable biopharmaceuticals," he says.

Dent says that since the launch of the anti-leukemia agent Myelotarg, which gained FDA approval in 2000, targeted protein drugs have become a reality, and all the evidence suggests that conjugated proteins are being increasingly recognised as exciting development targets. "Service providers in this field are now seeing this category representing 10-20 per cent of their biopharmaceutical workload, and probably the majority of biopharmaceutical executives interviewed in the past 12 months have plans for such products in their development portfolio. A deep knowledge base of the type offered by Fleet Bioprocessing will be essential in maximising the potential of this drug category – it will not be achieved by following standard generic methods or by buying off-the-shelf conjugation kits," he states.

Business strategy in the biopharmaceutical sector

Fleet Bioprocessing Ltd and Essential Science Ltd recently established a collaboration focused on the development and commercialisation of Fleet Bioprocessing's protein conjugation technologies within the European life science marketplace. Essential Science, founded in 2003 and headquartered in Glasgow, UK, supports technology exploitation to bring clients' technologies to market faster and more effectively. Dent says the collaboration will accelerate Fleet Bioprocessing's growth, providing the pharmaceutical industry with the service necessary to access its technologies rapidly and efficiently.

"Encouraged by the number of pharmaceutical clients making their way to our door despite our minimal exposure in that arena, we have made the biopharmaceutical sector a key market development target," he says. "Recognising our own lack of knowledge in this sector, we have identified Essential Science as a perfect business development partner.

"We are delighted to have finalised this arrangement with Essential Science. Conjugated protein therapeutics are increasingly being recognised for their impressive *in vivo* capabilities, and we believe our expertise in conjugation chemistry offers the opportunity for developers to arrive more rapidly at better product designs. Good drugs of this type are undoubtedly lying undiscovered due to the current lack of conjugation expertise in the sector. Essential Science is ideally positioned to help us develop our services in the pharmaceutical market."

"Fleet Bioprocessing's activities in the sector are still less than a year old, and so far a relatively small number of pharma clients have found out about our services – and our experience with them to date has definitely confirmed our belief that we have something to offer. Our collaboration with Essential Science is the cornerstone of our pharmaceutical market development strategy."

Longer-term prospects

"We are currently investing a lot of effort in developing this sector, and anticipate a steady growth in the business as pharma developers recognise that there is knowledge out there that could offer them currently unidentified druggable entities, speed their approach to market, and minimise manufacturability concerns," says Dent. "In the long term we are convinced that the value of this knowledge base, and the recognition that it can be most economically accessed on a contract basis, will continue to drive steady expansion in this sector."

Fleet Bioprocessing's core ability to add value is based on its skills in optimising conjugation procedures and transferring them into a manufacturing environment. However the company recognises that the value to clients will be increased if it can also offer a full package through to GMP manufacture, and it is actively exploring options for achieving this. Following the establishment of the Essential Science collaboration, the company expects to announce at least one further major alliance during 2005.

"Protein pharmaceuticals were fanfared for decades before they eventually broke through to become mainstream drugs," says Dent. "Targeted protein drugs, particularly for cytotoxics where therapeutic index is such a critical consideration, have lagged similarly behind the more optimistic predictions – but have now undoubtedly come of age," he says. "There seems to be a consensus that this is a growth area, and currently the focus of attention is in the development field, with the aim of achieving marketable pharmaceutical performance. This seems likely to remain the case over the next few years, but this will inevitably be followed by an increased focus on manufacturability and economics as more examples reach the market. All these factors are critically dependent on selection of the correct conjugation chemistries.

"There are other companies in the sector marketing specific conjugation technologies for given applications, for example Solulink and ConjuChem, and there is evidence that a few of the pharma players are investing the necessary effort in this area. Some clever things are going on in the most clued-up companies of this type, but will probably not become public knowledge for a year or two yet," he says.

"We believe that protein conjugation chemistry has the potential to offer an exciting new wave of biopharmaceutical candidates, and that – provided the appropriate effort is put into rational method development – these will be transformed into successful drugs," he concludes.

About This Article

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Alastair Dent, managing director of Fleet Bioprocessing, has a BSc in Chemistry from the City University, London. He has over twenty years of experience in conjugate development, validation and manufacture for companies including Amersham International, Kodak, and Johnson & Johnson. He is co-author and editor of *Bioconjugation* (Macmillan/Stockton 1998), a major reference work in this field, is on the committee of the Royal Society of Chemistry's Analytical Biosciences Group, and is a consultant in conjugation chemistry, process development and validation, and GMP.

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