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Biocompatibility of synthetic and bio-material fusion

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This communication proposes methods to improve the biocompatibility performance of synthetic materials for biological and biological material for synthetic applications. π-cloud extension by suitable ligand–ligand/metal–ligand interactions can make the synthetic–biological fusion suitable for such applications. The judicious use of ligands for π-cloud extension can be applied to carbon transformations and target-oriented drug delivery systems. Embedded metal-centre catalysts for synthetic–biological fusion include: (i) axial coordination via bridging ligands; (ii) ligands with weak to intermediate field strength and multidenticities; (iii) design of inert complexes, and (iv) development of multi-nuclear complexes.

Keywords: Biocompatibility, carbon transformation, drug delivery, sequestration, synthetic–natural fusion.

SYNTHETIC and biological materials can be used for many complex transformations in carbon management and target-oriented drug delivery systems. Carboxylation and reduction are two important reactions responsible for carbon management in nature. Eight biological pathways are known for converting inorganic carbon to organic material in cell biomass: (i) reductive pentose phosphate; (ii) Hatch–Slack cycle; (iii) Crassulacean acid metabolism; (iv) reductive citric acid; (v) 3-hydoxypropionate; (vi) dicarboxylate/4-hydroxybutyrate; (vii) 3-hydroxypropionate/4-hydroxybutyrate pathway and, (viii) reductive acetyl-CoA cycle. The first three are present in plant and some prokaryotes, 4th and 5th in bacteria, 6th and 7th in archaea and 8th in bacteria and archaea.

The choice of a carrier molecule is important in targetted drug delivery because it significantly affects pharmacodynamics and pharmacokinetics of drugs. Materials like lipids, natural and synthetic polymers, carbohydrates, surfactants and dendrimers are used as drug carriers[1–3]. The drug conjugate can be designed for improving its potential for complex π–π interactions towards the target moiety and drug[4–7].

Biological materials are eco-friendly, but they have limitation with regard to the proposed application as they are less durable in terms of mechanical strength and resistance to corrosion. Synthetic materials, on the other hand, have issues related to environment and biocompatibility in complex transformations. Metal complexes can serve

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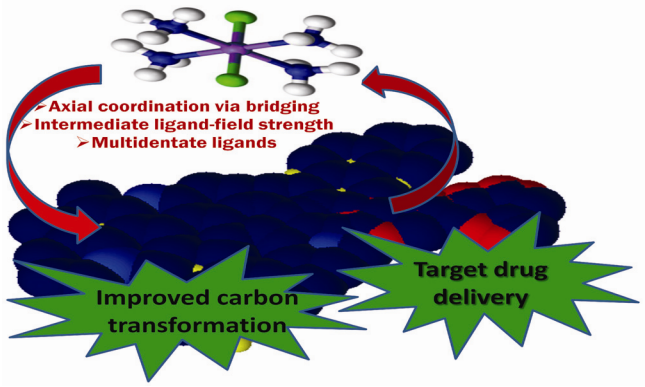
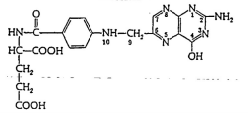
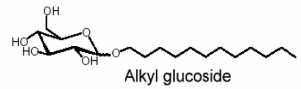
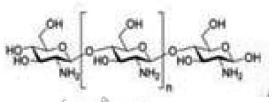
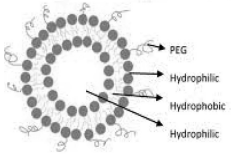
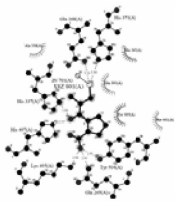
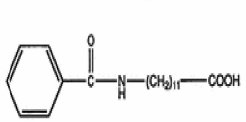
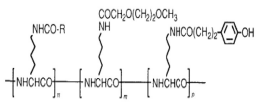
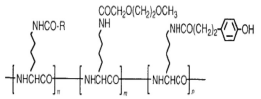


Figure 1. Synthetic–natural fusion.

Table 1. Hybrid fusion for carbon transformation

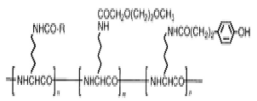
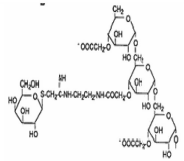
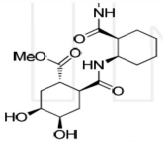
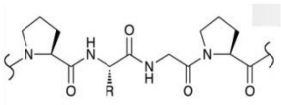
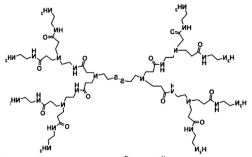
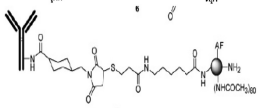
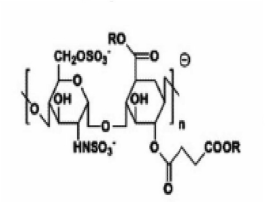
Pathways	Organisms	CO_2-fixing enzyme	Proposed complexes for chemical modification
Calvin–Benson Bassham cycle (reductive pentose phosphate cycle)[27,28]	*Oryza sativa*, *Nicotiana sylvestris*, *Nicotiana tabacum*, *Gossypium hirsutum*, *Solanum tuberosum*	Ribulose-1,5-bisphosphate carboxylase/oxygenase	Carboxylation: N-heterocyclic carbene (NHC) copper complexes; $Pd(OAc)_2$ with Cs_2CO_3
	Saccharomyces cerevisiae	Transketolase	
	Saccharomyces cerevisiae	Phosphoribulokinase	
Hatch–Slack cycle (dicarboxylic acid pathway)[29]	*Flaveria trinervia*	Phosphoenol pyruvate carboxylase	Reduction
	Saccharum officinarum	Malic anhydrase	
Crassulacean–acid metabolism[30]	*Bryophyllum tubiflorum*, *Sedum praealtum*	Phosphoenol pyruvate carboxylase	Electrocatalytic: Iridium dihydride pincer complexes and carbene-supported copper(I)boryl complex; CODH-modified TiO_2 nanoparticles
	Aptenia cordifolia	Malic enzyme	
Arnon–Buchanan cycle (reductive citric acid cycle)[31]	*Chloroflexus aurantiacus*	2-Oxoglutarate synthase	Photocatalytic: $Ru(bpy)_3^{2+}$/triethanol amine, $Ru(bpy)_3^{2+}$/methylviologen/ triethanolamine, $Ru(bpy)_3^{2+}$/ nicyclam^{2+}/ascorbic acid, FeTTP/triethylamine
	Aquifex pyrophilus, *Thermoproteus neutrophilus*, *Hydrogenobacter thermophiles*	ATP-citrate lyase	
	Advenella mimigardefordensis	Succinyl-CoA synthetase	
	Pyrococcus sp.	Fd-dependent pyruvate synthase/PFOR	
	Clostridium perfringens	PEP carboxylase	
Wood–Ljungdahl pathway (reductive acetyl-CoA pathway)[32]	*Moorella thermoacetica*	Acetyl-CoA synthase	Bpy-2,2′-bipyridine, Cyclam-1,4,8,11-tetraazacyclotetradecane, TTP-5,10,15,20-tetraphenylporphinato
	Clostridium thermoaceticum, *Methanobacterium formicium*	Formate dehydrogenase	
	Clostridium thermoaceticum, *Clostridium formicoacetium*, *Eubacterium acidaminophilum*, *Acetobacterium woodi*	5,10-Methylene-H_4 folate dehydrogenate	
	Clostridium thermoaceticum	Corrinoid	
	Carboxydothermus hydrogenoformans, *Rhodosprillium rubum*	CODH	
3-Hydroxypropionate[33]	*Chloroflexus aurantiucus*, *Metallosphaera sedula*	Propionyl-CoA synthase	
	Metallosphaera sedula, *Sulfolobus* spp.	Malonyl-CoA reductase Malyl-CoA lyase	
3-Hydroxypropionate-4 hydroxybutyrate cycle[34]	*Metallosphaera sedula*	Acetyl-CoA-propionyl CoA carboxylase	
	Propionibacterium shermanii	Methylmalonyl-CoA mutase	
Dicarboxylate-4-hydrobutyrate cycle[35]	*Clostridium aminobutyricum*, *Ignicoccus hospitalis*	4-Hydroxybutyryl-CoA dehydratase	

Table 2. Ligands for targeted drug delivery

Ligands	Ligand structure	Receptor	Target	Disease	Reference
Liposomes		Doxorubicin	Squamous cell lung	Carcinoma	36
Folate		Doxorubicin	Cancer cells	Epithelial cancer, myeloid leukaemia	4
Alkylglycoside		Sugars, alkyl and peptide moieties	Kidney membrane	Renal disorders	37
Chitosan		Doxorubicin conjugates with cis-aconityl linkage, paditaxel conjugates with succinate linkage	Colon	TNBS-induced colitis	5
Long-circulating (stealth) liposomes		Polyethylene glycol (PEG)	Tumour cells	Cancer	38
Angiotensin-converting enzyme mAb 989		Streptavidin (SA)–biotin bridge	Luminal surface of pulmonary vasculature	Cardiovascular and pulmonary diseases	39
Fatty acids (^{3}H-benzoyl adduct of lauric acid)		Albumin or galactosylated albumin/asialoglycoprotein receptor(ASGPR)	Hepatocytes	Liver disease	40
Saccharide-poly(L-lysine) galactose, lactose, *N*-acetylgalactosamine		Hepatic receptors	Liver	Liver disease	6
Saccharide-poly(L-lysine) mannosyl and fucosyl		Reticuloendothelial system	Liver, spleen and bone marrow	Liver and spleen diseases	6

(*Contd*)

Table 2. (*Contd*)

Ligands	Ligand structure	Receptor	Target	Disease	Reference
Saccharide-poly(L-lysine) xylosyl		Hepatic receptors	Liver and lung	Liver and lung diseases	6
Galactose and mannose		Glycosylated carboxymethyl (CMD)-dextran	Liver, parenchymal or nonparenchymal cells	Fibrosis and cirrhosis	41
Lectin		Sugar groups, salivery pellicle	Oral cavity/salivary mucins	Gingivitis, oral candidosis, oral lesion, xerostoma	42
Nucleic acid (Aptomers)		Doxorubicin	T-cell acute lymphoblastic leukaemia, T-cell ALL cells/PSMA protein on surface of prostate cancer cells	Acute lymphoblastic, myeloblastic leukaemias, malignant lyphomes, bronchogenic carcinomas	26, 43
Collagen		Antibiotics (gentamicine)	Adjancillary therapy, on-site delivery of antibacterial drugs	Treatment of prophylaxis of bone, wound healing, ophthalmic and periodontal treatment	43
Polyamine (PAMAM) folate dendrimer		Folate receptor	High-affinity folate receptor (hFR)	Ovarian tumours	44
Dendrimer		Anti-HER2mAb	Human epidermal growth receptor-2 (HER2)	Immunotherapy	45
Heparin folate paclitaxel (HFT)		Paclitaxel	Folate receptor (FR) expressing tumours (FR-positive human neck and head cancer cell line KB-3-1)	Human neck and head cancer	7

as highly efficient and commonly utilized catalysts or precursors for organic and biological transformations using the principle of bioorthogonal chemistry[8,9]. In nature, many bionuclear complexes with hydrophobic binding pockets show enhanced chemical reactivity towards the activation and transformation of small molecules such as CO_2 (ref. 10), and effect photosynthesis within a certain concentration[11]. It is therefore an appealing strategy to make use of embedded metal centres as modified biological and synthetic catalysts or precursors. This communication proposes methods to fuse synthetic and biological complexes to design efficient and biocompatible materials. The proposed fusion has the advantages in the upcoming research in carbon management and target-oriented drug delivery using the benefits of both biological and synthetic materials (Figure 1). The methods/protocols used to design embedded metal-centre catalysts for synthetic–biological fusion include the following.

(i) Axial coordination via bridging ligands can be an important strategy to connect synthetic and biological components. Axial coordination to Ni^{II} and Zn^{II} for *trans*-III cyclams is favoured in protein complexes via bridging ligands such as phthalate and is responsible for their biological activity[12–15]. Metal complexes are readily available for combinatorial synthesis of metal centres and ligand exchange. There are several examples of this fusion, such as insertion of symmetric metal complexes into the active site of apomyoglobin by binding to His93, which enables these new semisynthetic metalloenzymes to catalyse enantioselective sulphoxidation using the chiral protein cavity[16].

(ii) Ligands with weak to intermediate field strength and multidenticities may be suitable to design pharmaceutically acceptable metal carriers with embedded metal centres. To make hexamine cobalt $[Co(NH_3)_6]^+$ biocompatible, the four NH_3 ligands are replaced by ligands such as N_2O_4 or its isoelectronic moieties[17]. Furthermore, ligands with chiral centres can optimally tune the activity of metal centres towards their catalytic application in a living system[18]; and with some exceptions, aromaticity reduces cytotoxicity[19].

(iii) Metals exert structural roles, and inert complexes can be generally biocompatible. Free ion activity controls the bioavailability of metals, and complexation restricts metal activity. Similar biological activities are found in isostructural ruthenium and osmium complexes, and confirm the structural role of metals[20]. Labile metal complexes are more bioavailable and cytotoxic compared to inert complexes. Higher metal bioavailability makes the corresponding complex less biocompatible and vice versa[8]. Complexes with heavy metals, metals from the middle of the transition series or the third row down, or rare earth elements are preferred as a synthetic complex choice.

(v) Development of multi-nuclear complexes capable of forming an adduct with biomolecules. Improved bioactivity is found in tetranuclear ruthenium complexes compared to dinuclear complexes[21].

Ligand choices for this purpose are planar aromatic amines, alkyl amines, iminoethers, chiral dienes, amino acids, carbohydrates, steroids, alkaloids, small peptides and their isoelectronic entities. The above strategies can provide the optimal ligand for making biocompatible catalysts in order to optimize carbon management (Table 1). Synthetic–biological fusion can solve many problems in carbon sequestration by increasing the catalytic rate and/or oxygenase activity, improving plant photosynthesis, and making synthetic carbon transformations more efficient and eco-friendly.

Targeted drug delivery increases patient compliance efficiency of pharmaceutical agents through improved biodistribution and pharmacokinetics[22–24]. Synthetic–biological fusion can be used to design target-oriented drug delivery systems[4–7] (Table 2) by selecting appropriate π-cloud extension, such as estrogen moieties for targeting the breast, or xylylbicyclam, a potent anti-HIV agent that mobilizes stem cells (AMD3100, 'Mozobil') via targeting the 7-helix membrane receptor, CXCR4. Specific metallomacrocycle configurations can be recognized by proteins via metal coordination to specific amino acid side chains, H-bonding and hydrophobic interactions, allowing drug design optimization[25]. Nucleic acid (A10 RNA) ligands, aptamers and Dox which bind to the surface of prostate cancer cells have been used for targeted drug delivery[26].

The proposed fusion has the potential for scientific merger of different therapies (like Ayurvedic and allopathic medications) in cases where there is involvement of a metal either in the target or in the drug to develop effective medications with less side effects.

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