

Towards realizing nano-enabled precision delivery in plants

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Nanocarriers (NCs) that can precisely deliver active agents, nutrients and genetic materials into plants will make crop agriculture more resilient to climate change and sustainable. As a research field, nano-agriculture is still developing, with significant scientific and societal barriers to overcome. In this Review, we argue that lessons can be learned from mammalian nanomedicine. In particular, it may be possible to enhance efficiency and efficacy by improving our understanding of how NC properties affect their interactions with plant surfaces and biomolecules, and their ability to carry and deliver cargo to specific locations. New tools are required to rapidly assess NC–plant interactions and to explore and verify the range of viable targeting approaches in plants. Elucidating these interactions can lead to the creation of computer-generated *in silico* models (digital twins) to predict the impact of different NC and plant properties, biological responses, and environmental conditions on the efficiency and efficacy of nanotechnology approaches. Finally, we highlight the need for nano-agriculture researchers and social scientists to converge in order to develop sustainable, safe and socially acceptable NCs.

Industrial fixation of $N_{2(g)}$ and massive terraforming of the Earth's land mass have enabled sufficient food production for society, but current agricultural practices are unsustainable. At the same time, demand for food is increasing globally¹, while climate-related events (for example, heatwaves and drought) are predicted to decrease crop yields^{2–4}. Agrochemical inputs are also getting more difficult and expensive to source (for example, phosphorus and water), soils are being degraded and lost at rates higher than they are formed⁵, and crop pests are becoming more difficult to control with a warming climate. Greenhouse gas emissions from agriculture account for 14–28% of global greenhouse emissions⁴, further exacerbating climate change and the corresponding impact on crops. There is a tremendous need for disruptive technologies⁶ to overcome challenges to meeting future food demand and to meet

many of the 17 Sustainable Development Goals set forth by the United Nations, including zero hunger, climate action, and preserving life in water and on land.

Plant nanobiotechnology provides novel nano-enabled delivery approaches to improve the efficiency of agrochemical use, increase crop resilience and increase yields^{7–9}. Nano-enabled carriers (nanocarriers (NCs)), made of active agents (AAs) such as copper or zinc, and polymer, silica and carbon nanomaterials loaded with AAs, can improve plant resilience against disease, promote photosynthesis and protect plants against environmental threats such as heat and salinity stress^{6,8}. Application of nanoscale micronutrients increases their uptake and translocation by 20–60%, resulting in similar increases in biomass or yield^{9–11}. NCs can enhance the delivery of AAs, genetic

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Table 1 | Examples of targeted delivery of NCs and chemical cargoes in plants through biorecognition

Target	Surface moieties enable targeting	Nanocarrier	Designed functions	Ref.
Phloem	Sucrose	Carbon dots	Promote uptake and delivery of chemical cargo to phloem by β -cyclodextrin-functionalized carbon dots	18
	Glycine methyl ester	Polysuccinimide NCs	NC delivery of fungicide mediated by plant amino acid transporter AtLHT1	29
Stomata guard cells and trichomes	LM6M antibody/BSA	Gold nanoparticles	Nanoparticle delivery to leaf stomata and trichomes	27
Nucleus	Peptide (PKKKRKVKHKHKHKHKHKHKHKH/RRRRRRRRR)	Nucleus/cell-penetrating peptide nanocomplex	Improved nucleus internalization of cargo	30
Chloroplasts	Peptide (KH9-OEP34)	Organelle/cell-penetrating peptide nanocomplex	Improved organelle internalization of cargo	25,31
	Peptide (MASSMLSSATMV)	Quantum dots	Delivery of chemical cargoes by β -cyclodextrin-functionalized quantum dots into chloroplasts	12
	Peptide (MASSMLSSATMVGGGGGGKHKHKHKHKHKH)	Carbon nanotubes	Delivery of plasmid DNA-coated single-walled carbon nanotubes into chloroplasts	13
	Peptide (MASSMLSSATMVGGC)	Carbon dots	Delivery of chemical cargoes by β -cyclodextrin-functionalized carbon dots into chloroplasts	13
Mitochondria	Peptide (MLSLRQSIRFFKC)	Carbon nanotubes	Delivery of plasmid DNA-coated single-walled carbon nanotubes into mitochondria	16

material or anti-stress agents to specific biological targets, including plant leaves, roots vascular tissues and organelles (chloroplast and mitochondria)^{12–19}. However, there are many challenges to making these approaches efficient.

The challenges of using NCs to deliver nutrients or AAs in plants parallel those in nanomedicine. Over 30 years of research in nanomedicine can be leveraged for the design of precision delivery approaches for plants, including the development of biocompatible formulations, biotargeting principles and controlled release mechanisms^{20,21}, and pharmacokinetic models for assessing NC–cell interactions²², uptake, efficacy and toxicity. Recent studies have adapted approaches pioneered in nanomedicine to provide ‘targeted delivery’ in plants with some success (Table 1). However, there are important differences between precision delivery in plants and humans, leading to several key knowledge gaps that must be addressed.

- Plants have different cell barriers for nanomaterial uptake compared with mammalian cells, including cell walls, cuticle and mucilage. The cell walls made of cellulose, hemicellulose and pectin in plants are a crucial structural barrier that does not exist in mammalian systems.
- Biological targets in plants (for example, chloroplasts and phloem) are different to those in mammalian cells, requiring novel targeting biorecognition molecules.
- Therapeutic compounds and AAs for plants are different to those in mammalian cells, potentially requiring new NCs.
- The massive scale of agriculture necessitates the sustainable sourcing of low-cost materials for agrochemical delivery and for scalable manufacturing approaches. This will require innovation in both NC design and NC manufacturing.

There remain many unanswered questions about the phenomena controlling the complex interplay between NCs and the biological processes they affect in plants. NC–protoplast interactions²³ and targeting approaches are emerging^{12,15,16,18,24–31}. However, the fundamental processes controlling the interactions between NCs and important plant surfaces (for example, cell walls) and milieu of organic compounds in the vasculature (xylem and phloem) that may affect their uptake and translocation, transformation and efficacy are not known. There is currently no understanding of how plants respond to nanoparticulate

entities in their vasculature or ways to harness or control NC transformations in plants for beneficial purposes. Model experimental systems for probing the mechanisms of interactions of NCs with plant surfaces are not available. Computational approaches are also needed to predict NC transport or targeting in plants based on NC and plant properties. Developing solutions to these challenges will require the convergence of thought, approaches and technologies across disciplinary and societal boundaries. This Review discusses the critical technical challenges that must be overcome to realize high-value opportunities for nano-enabled precision delivery of agrochemicals and biomolecules in plants and presents a conceptual research roadmap to overcome those challenges.

NC structure–property relationships for active agent delivery

On the basis of lessons learned in nanomedicine, efficient NCs are those that interface well with organisms, readily overcome biological barriers (that is, extravasate from the vessels into target tissue and cells) and harness biological helpers (that is, disease-associated protein expression or changes in pH), and mitigate off-target effects. This is achieved by selecting appropriate material compositions and properties because they govern the fate of the NC in the biological system. These same properties are also integral to AA packaging, delivery and release. While some of the materials and chemistry concepts are transferable between these disciplines, the biology of plants and mammalian systems is distinct and the translational and commercialization space differs.

The multitude of factors influencing NC design for targeted and controlled release, size, rigidity, surface chemistry, aspect ratio and ligand density (Fig. 1) offer both opportunities and challenges. While this diverse design space provides a wide array of potential NCs for achieving efficient delivery in plants, the process of exploring this through trial-and-error or intuition-guided approaches is labour intensive. Machine learning strategies, such as those used in designing high-glass-transition polymers³², drugs and small molecules³³, self-assembling peptides³⁴, and lipid nanoparticles³⁵ can guide a more systematic exploration of the design space³⁶.

Material structure and surface chemistry define NC–plant interactions, uptake and translocation

Although systematic analysis of how NC properties influence interactions with plant surfaces and milieu is limited, available examples

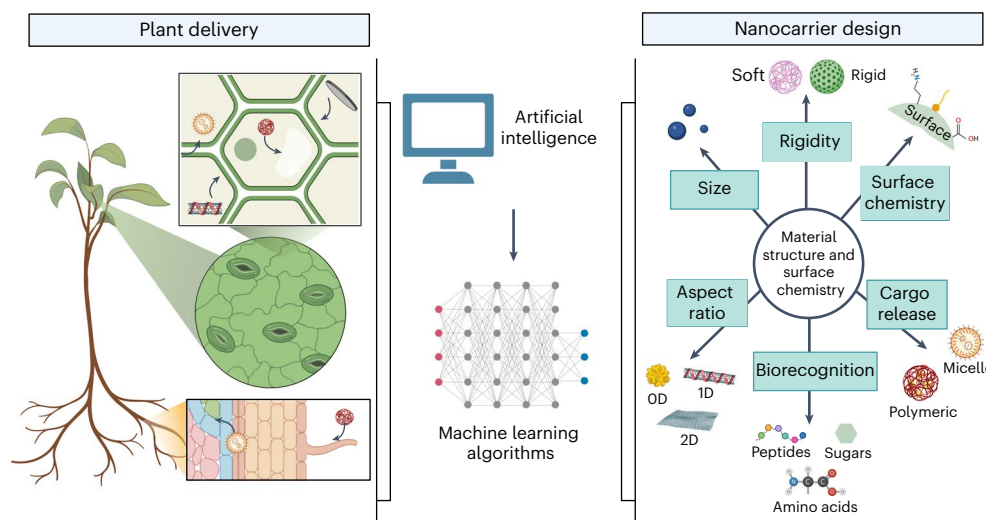


Fig. 1 | Design of NC properties (for example, size, rigidity and aspect ratio). Biorecognition molecules and surface chemistries determine the uptake, translocation and targeting of NCs in plants, as well as AA release mechanisms. Data-driven artificial intelligence (for example, machine learning) strategies will

need to work closely with experimental and modelling approaches to rapidly map relationships between NC structure and its function and identify the most promising unexplored NC candidates for precision delivery in plants.

provide insights into the engineering design space. Zeta potential magnitude determines the uptake of NCs across plant cell and organelle lipid membranes, with highly charged NCs being able to spontaneously disrupt and penetrate lipid bilayers^{23,37}. A negative zeta potential also facilitates the translocation of nanoparticles between organs through the vasculature, whereas positively charged nanoparticles tend to remain on the applied organs^{15,28,38}. Adhesion of particles to the cuticle on plant leaves is promoted by adding positively charged surface moieties³⁹.

Size, surface functionality and rigidity are also important controls of the efficiency of interactions with plant surfaces and the translocation of NCs across cell barriers. Many size exclusion limits (SELs) have been reported, for example, at least 50 nm for spherical gold particles through plant cell walls and cuticles of wheat¹⁵, <500 nm for cell membranes and <10 nm for symplastic transport in the plant cell via the plasmodesmata⁴⁰. While these SELs appear to severely limit the types and dimensions of possible NCs, these estimates were largely based on rigid materials. Less rigid (low stiffness), deformable polymeric NCs violate the aforementioned SEL cut-off^{41,42}. Relatively large (~10 nm in diameter and 200 nm in length), ‘soft’ (that is, less rigid) polymer NCs were taken up by leaves more readily than ‘hard’ metal and metal oxide particles of similar size⁴³ even though rigid inorganic nanoparticles have a lower energy barrier for membrane internalization than soft organic nanoparticles⁴⁴. As such, NC rigidity appears to be a key property affecting delivery across the plant cell wall⁴⁵. The chemical identity of the nanoparticle surface also has an important role in controlling interactions with hydrophilic and hydrophobic components of plant membranes^{15,26}. Polyphenolic compounds coating NC surfaces promoted adhesion and retention to the waxy leaf surface due to hydrogen bonding of the phenolic OH groups and the leaf cuticle⁴⁶. A better understanding of the mechanisms of uptake and translocation of nanoparticles in plants, especially for soft biomaterial interactions with plant surfaces, tissues and organs is needed to engineer effective NCs for plants.

Nanomedicine has demonstrated that low- and high-aspect-ratio materials have distinct in vivo trafficking and cell interactions, but this NC design variable is relatively unexplored in plants. Work delivering high-aspect-ratio carbon nanotubes and polymers in plants indicates that the smallest dimension of a high-aspect-ratio material controls its transport^{23,37}, and that there are differences between how monocots and dicots transport high-aspect-ratio polymeric NCs⁴³. Rods and

filaments or sheets, and in general materials with an aspect ratio >1, have a larger surface-to-volume ratio and therefore more contact sites with plant surfaces compared with spheres^{47–49}.

Biomimicry and bio-inspired designs

Biomimicry and bio-inspired designs and coatings can be leveraged to promote uptake and translocation in plants^{12,13,16,50}. Plant viruses, for example, achieve long-distance movement inside the infected plant through passive transport along with the photoassimilates⁵¹. Plant viral cell-to-cell movement is often achieved through specialized movement proteins, so there is an opportunity for biomimicry to promote the mobility of virus-like particles in plants. Coating NCs with biorecognition motifs (for example, peptides or sugars) can use specific cell receptors to promote uptake and translocation in plants¹⁸. For example, carbon dot-based NCs coated with guiding peptides or sucrose enhance the transport of chemical cargoes into chloroplasts or phloem, respectively, through biorecognition of transporters on their membranes^{13,18}. Similarly, zwitterionic properties of plant viruses have been leveraged to develop plant virus-based carriers for improved nematocide delivery through soil to plant roots^{52–54}.

Structure determines NC cargo and release to its target

We can leverage slow-release approaches from the medical community to provide controlled, stimuli-responsive, or on-demand release of AA cargoes in plants, but the formulation chemistry needs to be adjusted to the vastly different timescales for agriculture (days to months) compared with biomedical applications (minutes to hours, days or weeks). For instance, Bioclay nanosheets provided the slow release of double-stranded RNA in plants for several weeks and improved plant resistance to viral and insect pathogens^{47,48}. However, current approaches of electrostatic binding of plasmid DNA to NCs lack sufficient control over cargo release dynamics needed for DNA integration into the plant genome^{14,35}. The cyclodextrin molecules attached to small spherical carbon dots can be tailored to deliver a range of herbicides and pesticides¹³ by either slow or triggered release¹⁸.

Biologically or environmentally responsive NCs

Many adverse outcomes in agriculture are a result of environmental conditions, for example, heat stress, salt stress or water stress, that produce excess reactive oxygen species (ROS). There are also pH gradients (~5.5–8) across plant cells and organelles. Core-shell NCs

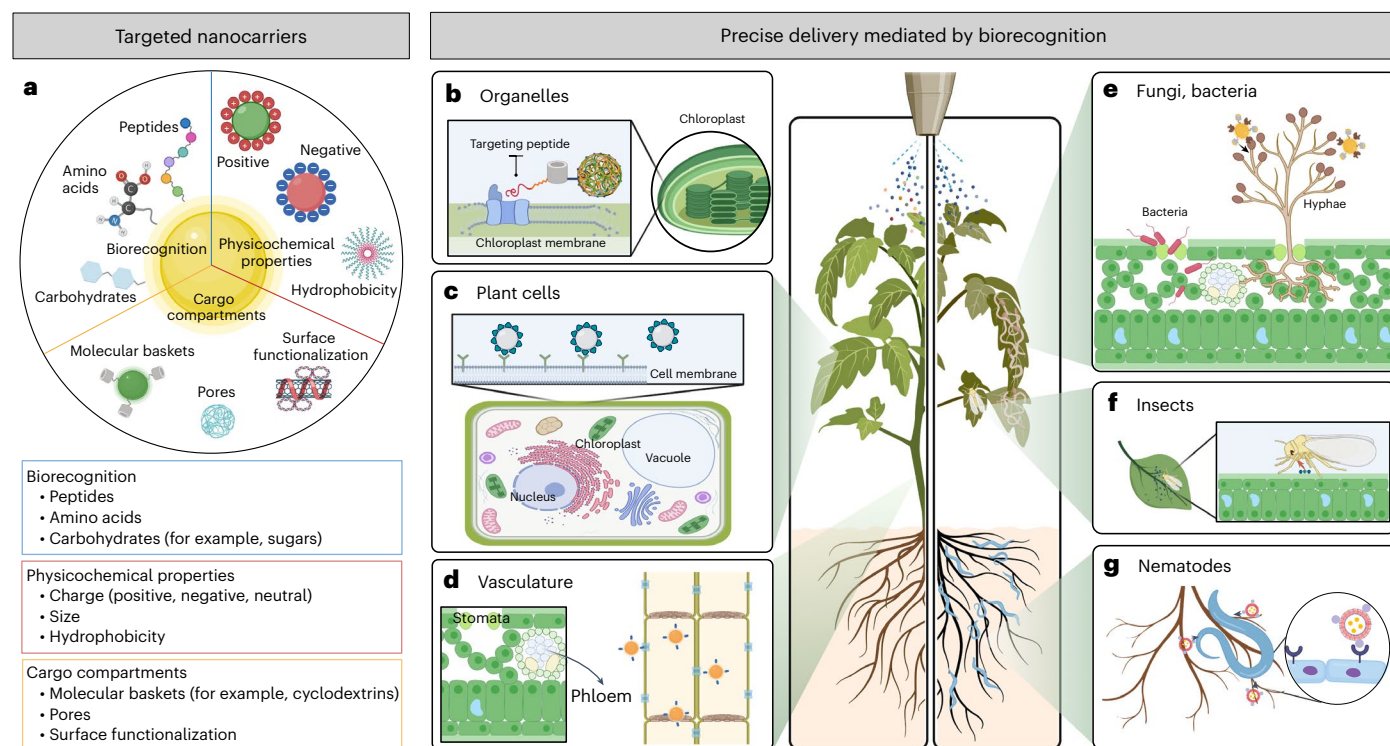


Fig. 2 | Precision delivery of NCs with cargoes to target organelles, cells and tissues mediated by biorecognition. **a**, NCs with cargo compartments are designed with physicochemical properties (for example, charge, size and hydrophobicity) and coated with biorecognition molecules (for example, peptides, amino acids and carbohydrates) for precise delivery to specific organelles, cells and tissues. The porous interior, molecular baskets or surface functionalization of the NCs enable the delivery of a wide range of AAs.

b–d, Biorecognition-mediated delivery of NCs and their cargoes to plant organelles (for example, chloroplasts; **b**), plant cells (for example, stomata or trichomes; **c**) and plant tissues (for example, phloem; **d**). **e–g**, NCs could also be used for biorecognition-mediated delivery to plant pests and pathogens, including fungi and bacteria (**e**), insects (**f**) and nematodes (**g**). Alternatively, NCs coated with pathogen-derived molecules could selectively recognize infected cells or tissues.

that respond to changes in, for example, pH, ROS or temperature, can deliver AAs to a specific location in the plant or in response to stress events. For example, nanocapsules can release nutrients (N, P, K, Cu) triggered by a fungal enzyme to increase photosynthesis in infected wheat and soybean⁵⁶, and temperature-responsive⁴³ or ROS-responsive⁵⁷ core–shell polymer NCs can deliver anti-stress hormones (spermidine) or photosynthesis enhancers (magnesium) only when plants are stressed, enabling the plants to manage climate extreme events.

Multi-staged NC designs where the structure–function is tailored towards each plant microenvironment could be envisioned, that is, a core–shell principle where the outermost layer is designed to facilitate plant surface attachment or entry—upon entry, functional moieties are exposed to facilitate long-distance versus cell-to-cell movement, targeting organelles and/or pathogens of interest, with subsequent release of cargo upon interaction with the target. A better understanding of the interactions of NCs with plant biological barriers, their in vivo transformations, biocompatibility and concentration-dependent effects on plants will be critical to designing effective NCs.

Biotargeting approaches for delivery of NCs and their cargoes

Biotargeting aims to deliver nanomaterials and their cargoes to specific plant tissues, cells or organelles, and plant pathogens^{13,16,27}. Biorecognition-mediated delivery relies on the ability to coat NCs with biomolecules such as peptides, aptamers, signalling tags and sugar adducts^{18,25,58} to guide them and their cargoes to specific plant or pathogen receptors or to desired plant cells or organelle surfaces⁵⁹. A complete understanding of the plant membrane properties shared

or differentiating target plant taxa will also be crucial for designing NCs capable of biotargeting⁶⁰.

Lessons learned from nanomedicine

Biorecognition-mediated drug delivery and immunoengineering approaches have been accomplished in nanomedicine by coating NCs with domains with high affinity and specificity for selected targets^{61–70}. Designing biorecognition molecules for targeted delivery in plants should be analogous to drug delivery methods in humans and animals^{12,71}. For example, identifying target molecules, such as tissue-specific proteins or surface receptors, could enable the design of NCs that preferentially bind to a targeted plant surface (Fig. 2). Predictive tools to design cell-penetrating biomolecules have been explored in nanomedicine but not in plants⁷². Binding studies of target moieties with protein affinity domains, nucleic acid aptamers, signalling tags and sugar adducts can create complementary pairs to specifically bind to the target tissues^{73–75}. Phage and yeast display, systematic evolution of ligands by exponential enrichment (SELEX), and thermal shift assays can also identify potential binding domains for improved specificity and performance^{73,76–78}. Adapting these tools for plants should enable the design of NCs for targeted delivery in plants.

Biotargeting approaches can also be used for efficient delivery of AAs to plant pathogens, including fungi, bacteria, viruses and nematodes that localize within the plant vasculature or roots. This approach has led to the development of multifunctional NCs for biomedical applications that can target multiple signalling pathways in infected cells, reducing toxicity and increasing therapeutic efficacy^{79,80}. Recent studies have indicated that NCs can be designed for targeted delivery to the surface of fungi cell-wall components^{81,82}

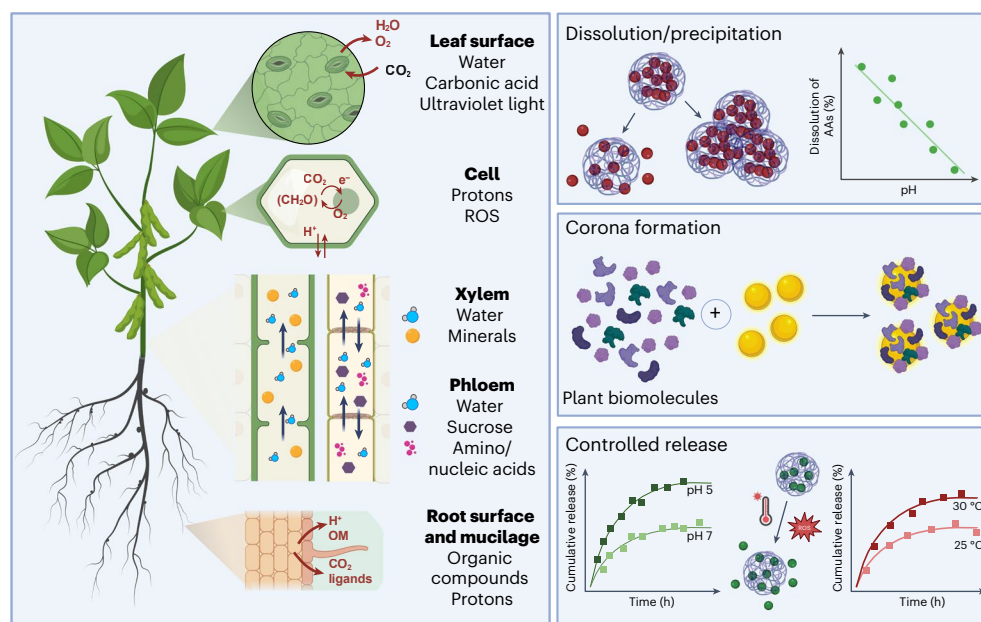


Fig. 3 | NC transformations for targeted and controlled release. NCs may transform in a myriad of ways on and inside plants. This includes transformations on the leaf and root surfaces after application (carbonic acid, UV light, organic matter (OM)), interaction with ROS in cells, or with components in the vasculature (dissolved minerals, sugars, amino acids and proteins). These

interactions can lead to dissolution and corona formation, and potentially trigger the release of the AA cargo, either intentionally or unintentionally. These transformations will ultimately control the fate of the NCs inside of the plants and the efficacy of the intended treatment.

or lipopolysaccharides on bacteria, enabling precise delivery of AAs^{83,84}. Plant immune receptors have also inspired the design of NCs for targeted drug delivery⁸⁵. NCs that are able to recognize pathogen-derived molecules could selectively target and deliver therapeutic agents to infected cells or tissues while avoiding healthy cells. Overall, receptor-mediated signalling mechanisms in plants⁵⁹ offer a powerful platform for advanced plant delivery systems through NC-mediated biotargeting strategies.

Targeted delivery mediated by the plant or pathogen biorecognition molecular machinery

Biorecognition-mediated delivery of NCs with chemical or DNA cargoes to specific organelles (for example, chloroplasts and mitochondria)^{13,16} or cells (for example, stomata)²⁷ has recently been demonstrated using guiding peptides or proteins that recognize specific receptors in the target organelle or cell membrane. Plant viruses encode unique multifunctional proteins (for example, movement proteins) with specific domains that interact with proteins from the host cells⁸⁶. The movement proteins facilitate the transport of virus-like biomolecules⁵⁰ by enlarging cell-to-cell connections (plasmodesmata), then use structural proteins for targeted delivery to specific sites in plants⁸⁷. The strategies that viruses use for penetrating and translocation inside plants can potentially be used to target AA delivery for disease control to specific organs, tissues or cells of interest where pathogens infect or colonize. This could increase AA efficacy and reduce application doses of environmentally toxic pesticides. However, we currently have a poor fundamental understanding of the delivery mechanisms by biorecognition in plants, the physical and chemical interactions of NCs with plant interfaces, and the potential side effects of biotargeting on plant (or non-target organisms) physiological and developmental processes.

NC transformations for targeted and controlled delivery

Experience with nanomedicine indicates that in vivo NC transformations, for example, biocorona formation⁸⁸, dissolution or enzymatic

degradation, are critical in controlling both targeting and AA delivery efficacy. NCs will interact with a plethora of biomolecules on plant surfaces (for example, lipids in membranes and pectin/cellulose in cell walls) and in plant cytosolic, apoplastic or vascular fluids. Yet, the range of transformations of NCs (Fig. 3) once they are on or inside plants remains largely unexplored.

Exogenous transformations at the plant's outer surfaces

The cuticle, a hydrophobic plant surface that prevents water loss from plants, is the first key biointerface encountered by foliar-applied NCs. Root peripheral and border cells are the first biointerface encountered by soil or hydroponically applied NCs. Both barriers can promote the dissolution of kinetically unstable NCs^{49,89,90}. The rhizosphere (the interface between soil and roots) has gradients of physical and chemical conditions due to root exudates (carbon-based biomolecules) that can promote NC transformations. For instance, wheat plant root exudates led to a pH increase in rhizosphere soil that modulated the proton-induced dissolution of CuO NCs⁹¹. Dissolution of Fe-Al/Ge nanotubes⁹² and CuO NCs⁹³ by plant-derived siderophores has been reported. By tuning the rate of NC dissolution, or by engineering the materials to specifically interact with biomolecules on these interfaces, can control the rate of delivery of these agents into plants⁴⁹. Overall, a better understanding of the range of biomolecules in leaves, roots (for example, root exudates) and stems that interact with and mediate the transfer or complexation of NCs is needed to design efficient materials⁹⁴.

Endogenous transformations inside of plants

Uptake of NCs into plant cells relies on the translocation across cell walls. The cell wall is the outermost layer of plant cells, formed by a complex mixture of cellulose fibres, pectin and other biomolecules depending on the plant species. The underlying chemical and molecular-level transformations of NCs within cell walls or cell membrane components, and how they affect their subsequent translocation or interactions with plant biomolecules such as lipids, carbohydrates or proteins, are unknown. As whole-plant translocation requires that the NC cross a cell

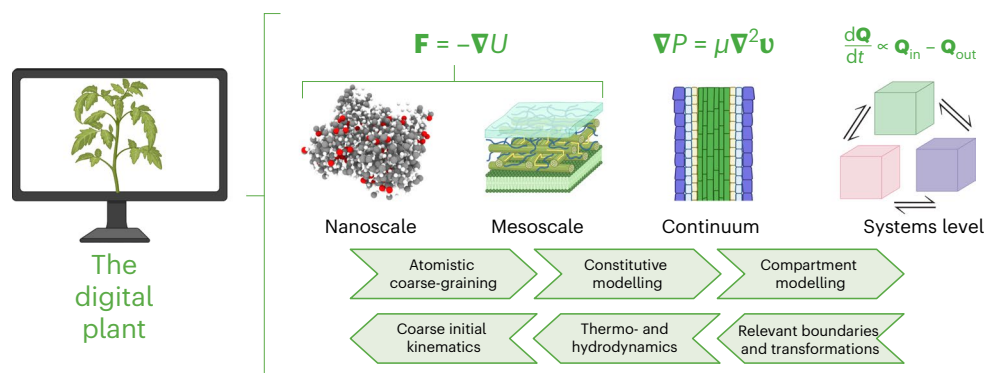


Fig. 4 | Development of a plant digital twin will enable rapid discovery of NC designs that enable efficient targeted delivery into plants. It will require the integration of models at different scales that capture the relevant biochemistry and biophysics at the NC–plant biointerface. At the molecular scale, a core modelling approach is molecular simulation, including molecular dynamics simulation, which is driven by interatomic forces F that are computed from the gradient ∇ of the

interatomic potential U . Important continuum-scale models include low-Reynolds-number hydrodynamics, which relates the gradient of the fluid pressure P to the viscosity and the Laplacian ∇^2 of the velocity u . At the systems level, models focus on overall flows Q in and out of appropriately defined compartments over time t . Parameterizing those models will also require development of model plant surfaces for detailed mechanistic studies both in vitro and in vivo.

wall and membrane, NCs translocating through the plant vasculature have probably acquired a biocorona^{23,37,95} further altering the designed surface properties. Reports on the interactions between plant proteins and NCs are limited^{96,97} and the impact of these transformations on translocation and biotargeting is unknown. Systematic studies are needed to understand how NC properties such as size, charge, chemical identity and hydrophobicity impact the formation of plant protein coronas and subsequent NC translocation, targeting and efficacy.

Controlled release by NC transformations

Large swings in pH as NCs translocate in plants can potentially be leveraged to elicit a transformation for targeted release of an AA. For example, leaf-surface pH changes during formation of carbonic acids enabled the slower release of double-stranded RNA from Bioclay nanosheets for combating plant pathogen infections⁴⁸. Apoplastic fluids can be acidic (pH of 5.5–6), while the pH in the cytosol and chloroplasts is slightly basic (pH of ~7.5–8). Although a pH-triggered release is common in biomedical applications, they have been underutilized for delivery of AA in plants. The generation of ROS or reactions with sulfur-based analytes in the glutathione pathway can also be used for triggered and targeted AA release, but few studies have explored these approaches⁵⁷.

Challenges for delivery mediated by transformations

There is a limited understanding of the acquired coatings of biomolecules on NCs and how this affects their transformation and biotargeting in plants. Categorizing the fundamental interactions of NCs with the wide diversity of proteins and biomolecules in plant species will require a large set of model systems. The in vivo characterization of these processes is even more challenging to explore given the difficulty in extracting plant phloem and xylem sap in sufficient quantities for study and the lack of tools for measuring NC transformations in vivo. In addition, these interactions will probably be modulated by the plant life cycle as well as by responses to biotic and abiotic environmental conditions.

Creating predictive digital model plant systems

The development of a plant ‘digital twin’, that is, a virtual (computer-based) representation of a plant, including its biosurfaces, organs and vasculature is a potentially transformative tool for enabling targeted delivery of NCs in plants. Digital twins have been widely used in manufacturing, infrastructure management and predictive maintenance^{98,99}, but there is no existing plant digital twin to virtually test the efficacy of various NC biotargeting or controlled release strategies. Creating such a model would enable rapid in silico design and testing of

different NC configurations for a specific function, for example, enhanced delivery of an AA to a target site within the plant. The concept of the plant digital twin is analogous to the ‘digital patient’ concept in personalized human medicine, that is, computational fluid dynamics (CFD) in support of patient-specific stents or patient-specific prostheses^{100,101}. In both cases, the goal is to numerically simulate physical laws governing transport and chemical phenomena (for example, adsorption, advection, diffusion or transformation) with geometries and boundary conditions specific to the individual under consideration. These models are intrinsically multiscale, integrating knowledge from the atomistic scale (for example, molecular transport across cuticular membranes or within ion channels)^{102,103} to the continuum scale (for example, pressure-driven flow within the phloem or cohesion-tension driven flow within the xylem)^{104,105}.

Key enabling computational methodologies

There are several computational frameworks that need to be developed as the backbones for a digital plant model (Fig. 4). Each framework provides information at different length and time scales, as nanoscale, mesoscale, continuum and system level.

Nanoscale

Molecular dynamics and Monte Carlo simulations can be used to model nanoscale (for example, tens of nanometres and timescale of nanoseconds to microseconds) transport phenomena¹⁰⁶ such as transport of NCs across plant biointerfaces. Both molecular dynamics and Monte Carlo require molecular-scale knowledge about material compositions, microstructures and mechanics. While these properties can be determined for the NC using available analytical techniques, the molecular-scale properties of plant surfaces, such as the cuticle, cell wall, epidermis and so on, are less certain and variable across plant species. Atom simulations based on classical molecular mechanical force fields¹⁰⁷ may potentially be used to simulate important transport phenomena or chemical transformations on the order of thousands of atoms¹⁰⁸, but the amorphous microstructure of biological materials will make it challenging. A critical step in the application of such simulations to plant surfaces will be the parameterization and validation of the force-field parameters for the relevant components.

Mesoscale

Coarse-grained molecular dynamics simulations using the MARTINI model¹⁰⁹ have lower resolution, but are typically two to three orders of magnitude faster than corresponding all-atom simulations, making it possible to simulate substantially larger systems (for example, a

patch of cytoplasmic membrane at the length scale of ~100 nm¹¹⁰, and for much longer timescales than all-atom simulations. Similar models at comparable or even lower resolution¹¹¹ have been developed for plant cell walls¹¹² and used to explain their unique mechanical properties¹¹³.

Continuum

Many plant transport systems can be modelled using classical transport laws (for example, Navier–Stokes), so there are a range of continuum CFD methods that are suitable for studying transport in plants. For example, finite-element-based approaches have been used to model transpiration in stomata¹¹⁴ and flows within xylem¹¹⁵; finite-volume-based approaches have been used to model root uptake of water and nutrients^{116,117} and hydrogen peroxide signalling within plants¹¹⁸. Flows into and within plants may show phenomena that pose unusual modelling challenges, including multi-phase flows (as is the case in transpiration), free surfaces (as is the case for droplets on a leaf) or geometrically complex boundary conditions (as is the case for flows in xylem and phloem). In such cases, other CFD approaches may be fruitful, including the lattice Boltzmann method, which has been used to model porous flow through bordered pits in xylem (a system that presents particularly complex boundary conditions)¹¹⁹.

Systems level

A particularly useful advance for modelling targeted delivery in plants would be the development of botanokinetic/botanodynamic (BK/BD) models, in close analogy to pharmacokinetic/pharmacodynamic (PK/PD) models for drug delivery in humans¹²⁰. Similar to a PK/PD model, a BK/BD model would interface with all of the previously discussed simulation methodologies to describe the movement of NCs within and between various compartments of a plant (for example, a plant's cuticular membrane, organelles such as chloroplasts, or the rhizosphere). Developing the necessary general-purpose BK/BD computational tools will enable efficient optimization and sensitivity analysis¹²¹, a necessary feature to enable rapid discovery of new NCs and targeted AA delivery approaches.

Benchmark data to develop and calibrate digital plants

Modelling the behaviours of NCs in plants will require the collection of benchmark quantitative data on plant surface properties to calibrate and validate those models. In particular, it will be necessary to quantify the structural composition and properties of selected surfaces, for example, the chemical composition of plant cell wall and cuticle surfaces, organelle membranes and endomembranes. In addition to the chemical composition and structural features of plant surfaces, it might also be necessary to include the mechanical properties of plant surfaces in plant–NC interaction models. For example, the mechanical properties of plant surfaces such as tensile strength¹²², contact angle, porosity and roughness may predict the movement of NCs through key plant barriers. Some can be measured using existing techniques (for example, contact angle of a leaf cuticle), but measuring these properties *in vivo* for internal structures, such as cell walls, will be challenging. In addition to the physical and chemical properties of important plant surfaces, the properties of phloem and xylem that may affect transport in the plants must also be measured. For example, the rheological properties of these fluids would be needed to accurately model sap flow transport rates as well as diffusion between cells or across plant biosurfaces¹²³. While many of these properties are available in the plant biology literature, quantitative measurements of the interactions of NCs with plant biosurfaces are limited yet necessary for the development and calibration of plant digital twins. It is also worth emphasizing that, as is the case for all digital twins, useful digital plants would necessarily require extensive calibration and validation, at all scales studied by the model. A high near-term priority is the

development of canonical experiments that can be used to validate digital plant models.

Critical challenges for the development of digital plants

The development of a viable plant digital twin for studying NC behaviours *in vivo* is a daunting task. This is especially true given the range of plant biological diversity. For example, there is an enormous range of cuticular compositions and microstructures¹²⁴ and a large diversity in plant vascular structures¹²⁵. A fruitful starting point may be to develop representative models for broad groupings of main crop plants that have well-characterized differences in relevant anatomical features (for example, monocots versus dicots, C₄ versus C₃ photosynthesis)^{126,127}. Another critical need for building digital plant models will be the development of open-access simulation codes and datasets, including complex datasets from -omics (for example, genomic, proteomic, metabolomic) analyses. It will be particularly important to develop consistent formats and standards for workflows, data and metadata, which will require significant collaboration (and some amount of enforcement) within communities of researchers, publishers, funding agencies and industrial partners. On this front, it may be particularly instructive to look at the successes of and challenges faced by analogous efforts to digitally twin materials, exemplified by the Materials Genome Initiative^{128,129}.

New data acquisition approaches for tracking NC delivery

Development of new tools, capabilities and model systems will be critical to development of a plant digital twin and realizing the benefits of nano-enabled precision delivery of agrochemicals (Fig. 5).

Tools for *in vivo* characterization and detection of NCs

Methods for imaging NCs *in vivo* are available but have limitations. For example, NCs can be tracked using their intrinsic fluorescence^{12,13,95}, or a labelling dye^{130–133}. NCs can also be tracked using selected elements in the NC using laser ablation¹³⁴ or inductively coupled plasma mass spectrometry (ICP-MS)^{15,135}, synchrotron X-ray fluorescence (XRF) imaging^{15,27,28,136,137}, or electron microscopy with energy dispersive X-ray analysis¹³⁸. However, most of these tools are destructive and provide only two-dimensional information. Three-dimensional information is often needed to assess the ability of an NC to pinpoint selected targets, for example, chloroplasts. Here, X-ray tomography, magnetic resonance imaging (MRI) and confocal microscopy tools can provide three-dimensional reconstructions. They can also be used *in vivo* and *in planta*^{12,13,139}. All of these methods may require a higher mass of NCs than exists in the plant tissues, so approaches to increase the sensitivity of these methods are still needed.

Tracking NC transformations *in vivo* is also a challenge, but some tools exist. Changes in speciation of inorganic NCs can be measured using synchrotron X-ray absorption spectroscopy¹⁴⁰ or isotopic tags¹⁴¹. Techniques such as Fourier-transform infrared (FTIR) spectroscopy, Raman spectroscopy or microparticle-induced X-ray emission (μ-Pixe) can be used for tracking NC surface modifications and interactions with functional groups on a plant surface¹⁴². Gaining a deeper understanding of NC transformation and persistence in plants may require extracting and isolating the NCs before they are characterized using single-particle ICP-MS^{143–145}, single-particle ICP-time-of-flight-MS¹⁴⁶ or three-dimensional excitation emission matrix spectroscopy¹⁴⁷. These techniques also all have different limits on sensitivity, spatial resolution and the NC size range that may be observed. They also require extraction from the plant, which may alter their properties before analysis, leading to artefacts. Methods that avoid these artefacts need to be developed and validated.

Increasing the throughput and speed of data acquisition from *in vitro* plant cell and tissue-based systems

Characterization of the distribution of delivered NCs in plants is currently limited by the low throughput of using whole plants. Inspired

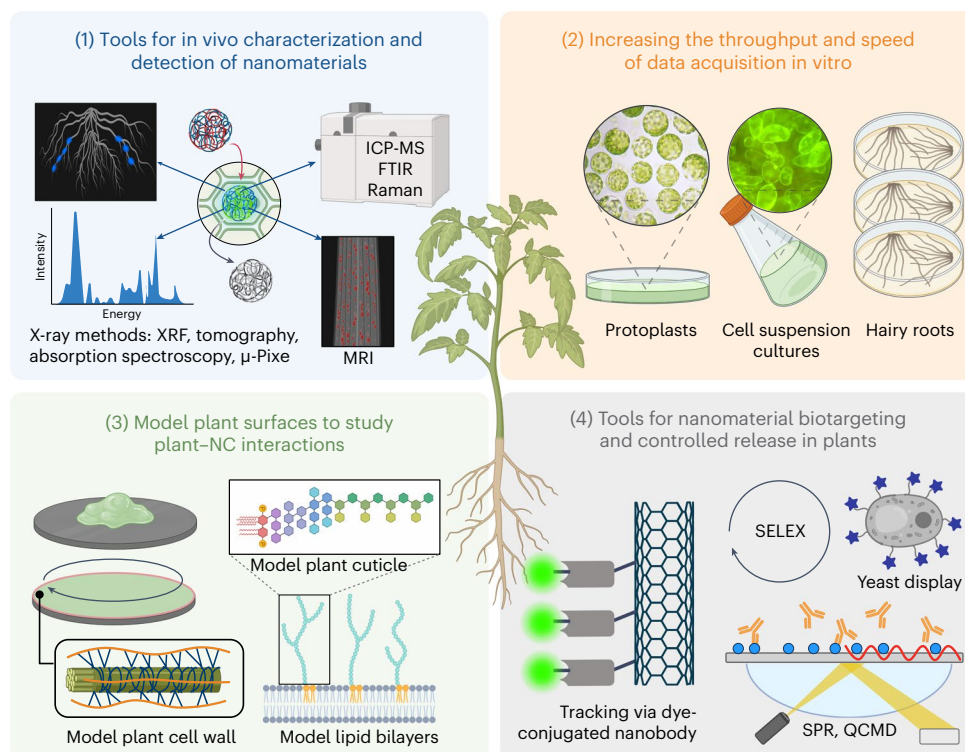


Fig. 5 | New tools and technologies needed to design NCs for precision agrochemical delivery. These include new methods for the (1) in vivo characterization and detection of NCs in plants, (2) increasing the throughput and speed of data acquisition via in vitro plant systems, (3) model plant surfaces to characterize NC–plant interactions and (4) NC biotargeting in plants.

by biomedical research, the study of plant–NC interactions should utilize in vitro plant cell and tissue model systems to significantly increase throughput and data collection. Examples of in vitro plant systems include protoplasts¹⁴⁸, cell suspension cultures¹⁴⁹ and hairy roots^{150,151}. Protoplasts are individual plant cells devoid of cell walls. They are isolated from plant tissues followed by either mechanical or degrading enzyme cell-wall removal. From a small amount of tissue, $\sim 10^8$ cells can be quickly obtained, which enables rapid testing of how NCs interact with plant cell membranes, where they localize intracellularly, their cellular toxicity and the transformations they experience in plant cells, such as protein, carbohydrate or lipid corona formation. The limitations of protoplasts are that important cellular internalization information may be missed given the lack of cell walls, and lack of feasibility of long-term studies due to the short life span of protoplasts. Plant cell cultures are an alternative approach. They are formed by cells with walls, a key barrier for NC entry, and under optimal conditions in a liquid culture can divide and propagate indefinitely¹⁵². Plant cell cultures have been used to investigate carbon nanotube and quantum dot toxicity^{153–156}, and can potentially be used to elucidate interactions of NCs with native plant cell walls in a high-throughput manner¹⁵⁷. Hairy roots, created through genetic transformation using *Rhizobium rhizogenes*, are plant root tissues that can be maintained in culture and mimic natural root anatomy and function^{151,158}. They are routinely used for answering fundamental plant cell and root biology questions^{159–161}. Hairy roots could provide a useful platform for assessing NC–root surface interactions or NC transport and transformation in plant tissues.

New model systems for studying plant surface–NC interactions

Experimental model plant surfaces are also needed to elucidate the mechanisms of NC–plant biosurface interactions. While not yet widely available, some examples exist. Model plant cuticle layers were designed using self-assembled monolayers with specific biomolecular

composition to understand how cationic copper oxide nano-spikes helped adhere those NCs to plant leaves⁸⁹. Model cell walls made of cellulose, lignin and pectin were created on quartz crystals to understand the chemical interactions between NCs and cell walls¹⁶². Similar approaches can be used to explore how structural defects in the cuticle or cell walls, or natural openings on the plant surface such as trichomes, will affect NC uptake and translocation. Model plant lipid bilayers such as sulfoquinovosyl diacylglycerols, a novel model chloroplast membrane, can be constructed to study the association of NCs with and uptake across cell membranes using quartz crystal microbalance with dissipation monitoring (QCM-D)⁶⁰. Future opportunities could include generation of more representative and complex plant tissue platforms, such as plant organs-on-a-chip with multiple organs—for example, high-throughput platforms with both roots and shoots enabling the study of NC uptake and translocation and delivery of agrochemical cargoes.

Tools for studying NC biotargeting and controlled release of cargoes in plants

Techniques used in the biomedical field for intra- and intercellular NC tracking and drug delivery discovery could be adapted for tracking NCs in plant tissues and organelles. For instance, nanobodies—smaller variants of antibodies (2–4 nm)¹⁶³ with high affinity to an NC can be conjugated with markers (for example, fluorophores or radioactive elements) for NC visualization in planta. Similarly, SELEX platforms can be used to identify aptamers (short single-stranded DNA or RNA molecules) that selectively bind to a specific target¹⁶⁴. Furthermore, there are existing screening tools to build targeting libraries of plant biomolecules and chemicals and their binding domains using techniques such as phage and yeast display, molecular docking or other adsorption/binding assays (QCM-D) on tissue extracts, whole cells, pathogens and bioinformatics tools^{165,166}. This would facilitate the creation of databases of potential biomolecules for biotargeting

applications in plants. In silico approaches using artificial intelligence programs such as AlphaFold¹⁶⁷ and machine learning to predict protein structures and plant biomolecule interactions could allow virtual screens for putative binding domains and de novo design of NC tracers for biotargeting research. However, the accuracy of in silico methods still needs to be validated by experimental approaches, as these predictive algorithms have limitations (for example, determining conformations of intrinsically disordered proteins)¹⁶⁸ and cannot yet fully replace experimental structure determination¹⁶⁹.

Sustainable development and use of NCs in agriculture

Convergence across scientific and societal boundaries to foster sustainability

Improving the sustainability of agriculture is a complex socio-economic problem that requires integration of expertise from diverse academic disciplines and from critical non-academic stakeholders to create combinatorial methods and courses of enquiry^{170,171}. The merging of knowledge to spur critical innovation in nano-enabled agriculture will require methods for designing and managing convergent research approaches in large, complex scientific endeavours; examples include interdisciplinary studies¹⁷², the science of team science¹⁷³, and integration and implementation sciences¹⁷⁴. Authentic co-production of knowledge with diverse stakeholders across the entire innovation-to-implementation cycle, from the inception of formulating questions and throughout investigation and translation, is critically important to its success¹⁷⁵. Viable, sustainable solutions will emerge only if ideas, approaches, technologies and human systems understanding across a broad range of perspectives are harnessed, combined and communicated intentionally and inclusively to fuel critical innovations.

The products or processes designed to improve food and agricultural production systems, their development, manufacturing, production, use and deployment also need to be sustainable. Perspectives and expertise from social sciences, humanities and an array of non-academic partners, as well as considerations of human and environmental health, societal and ethical implications, and technological and economic considerations¹⁷⁶, must be included in formulating the research questions from inception^{177,178}. Meeting the expectation will require application of team science methods to advance transdisciplinary objectives. Intentionally inclusive approaches are also needed to develop and use nanomaterials for agricultural production, adhering to core concepts of sustainability and responsible innovation^{179–181}.

NC scalability and manufacture

The enormous scale of global agriculture makes process scalability critical for commercial manufacture of any proposed technology¹⁸² so barriers to scalability must be considered early in the development process. For example, microfluidics techniques used in developing nanomedicines are fundamentally limited to scale-out (that is, many small-scale units running simultaneously) rather than scale-up, which is usually prohibitively expensive and inefficient. As a result, only a handful of nanomedicine formulations have reached the market¹⁸³. The nanomedicine field provides useful metrics for success in agrochemical nanoformulation development and research, including AA loading and encapsulation efficiency. AA loading, that is, the mass of AA per mass of delivery vehicle in the formulation^{184,185}, must be high to achieve a desired dose of the AA while minimizing excipient mass that may have undesirable effects¹⁸⁶. Encapsulation efficiency, that is, the mass of AA encapsulated in a delivery vehicle per mass of AA introduced into a formulation process, should be maximized to reduce manufacturing waste and cost because the AA may be the most expensive material in a formulation and recovery and recycling of unencapsulated AA may not be possible.

Understanding risk and impacts on the environment and society

Researchers, innovators and other stakeholders must strive to avoid mistakes of the past and avoid collateral or unintended consequences from rushed application of new technologies by better understanding potential risks of nano-enabled applications and incorporating stakeholder needs and perspectives into research and development¹⁸¹. For nano-enabled agriculture, this includes assessing the environmental fate and potential toxicity and ecotoxicity of the NCs in different environmental matrices (for example, soil, water, sediment), assessing the effects of these materials on soil properties and function¹⁸⁷, and researching growers' and consumers' perceptions of NCs in agriculture^{181,188,189}. For example, stakeholders are more supportive of nanotechnological innovations for agriculture with greater benefit-to-risk ratios¹⁸¹, for example, nano-ZnO₂ used to combat citrus greening and nanovaccines used to decrease rates of *Salmonellosis* in egg-laying hens were viewed favourably, while the use of nanomaterials for food improvement, for example, nano-TiO₂ to whiten infant formula, were not. This approach can avoid the reluctance of adoption of novel technologies in food and agriculture systems, such as occurred for the first generation of genetically modified organisms that were implemented without adequate inclusion of interested parties¹⁹⁰. For example, the use of degradable biopolymers^{191,192} in place of non-degradable synthetic polymers used widely in agriculture for seed coatings, slow-release fertilizers and plastic film mulching, but with the same functionality, would alleviate concerns about toxicity and persistence and promote adoption^{193–195}.

The scale of agriculture also means that materials used for agrochemical delivery must be sustainably sourced. For example, agriculture generates large amounts of 'waste' lignocellulose that can be used to prepare biodegradable nanomaterials¹⁹⁶, and seafood waste can be used to derive natural, biodegradable biopolymers (for example, chitosan) for NC use¹⁹⁷. Carbon dot NCs for agrochemicals can be manufactured from a range of agricultural wastes including plant or animal derivatives, including leaves, stems, husks and urea^{13,198,199}, and silica extracted from husks can be used for seed treatments to enhance germination^{200,201}.

Regulatory landscape and challenges for nanotechnology mediate delivery approval

New technologies will undergo regulatory scrutiny, and this is especially true for NCs. Formulating NCs from materials that are generally regarded as safe (GRAS), such as certain biopolymers and virus-like particles, would also help in the regulatory process. While some inorganic NCs have raised concerns regarding their potential toxicity to consumers²⁰² or to plants, biomolecule-based NCs can potentially be more biocompatible and biodegradable than inorganic or synthetic counterparts, and more acceptable to stakeholders.

Outlook

Nano-enabled precision delivery of AAs in plants will transform agriculture, but there are critical technical challenges that must be overcome to realize the benefits of this suite of technologies. The relationships between the structure and surface properties of NCs and their interactions with plant surfaces and biomolecules, and their ability to carry and deliver the desired AA must be elucidated to enable bio-inspired NC designs. Multifunctional NCs employing biotargeting approaches adapted from nanomedicine could precisely deliver nutrients and AAs to specific plant tissues, cells or organelles, enhancing the effectiveness of nano-enabled applications such as genetic modification by delivering gene-editing tools (for example, plasmid DNA, RNA and CRISPR–Cas9). However, realizing these benefits will require a greater understanding of the range of biotargeting tools available, their mechanisms of action and biotransformation, and the potential for any undesired detrimental impacts on plants. Better understanding of how NC

transformations in plants affect their efficacy or targeting could be leveraged to design reliable delivery and targeting strategies. The fate of NCs internalized into plant tissues also needs to be considered in their design. While many NCs that are applied to plants may transform²⁰³, the transformation products are likely to persist in plant tissues and soils unless they are biodegradable. Current tools used to assess the fate and life-cycle impacts of NCs do not include these considerations and must be adapted for this purpose²⁰⁴.

The development of new NCs for nano-enabled precision delivery is hampered by the lack of high-throughput screening methods and by the absence of predictive models. A multiscale plant digital twin that captures important NC–plant surface interactions and biotargeting chemistry could be used to virtually screen for the efficacy of numerous different combinations of properties to guide and accelerate NC design and development. Developing such models will require new *in vivo* tools to detect and characterize NCs and *in vitro* tools to rapidly quantify the interactions of NCs with important plant surfaces. It will also require a better understanding of plant physiological responses to the presence of the NC, a formidable challenge given the diversity of plant species, growth cycles and potential environmental conditions to explore. This Review discussed the development of digital plants from the scale of molecules to organisms. A digital plant model at this level of organization could potentially be incorporated into already existing crop or ecosystem models²⁰⁵ to simulate NC and environmental interactions at a larger scale. Overcoming these scientific challenges to develop globally sustainable nano-enabled precision delivery approaches will require convergence across both scientific and societal boundaries.

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G.V.L., J.P.G., N.F.S., K.D.R. and C.O.H. conceived the idea for the workshop and resulting paper. All authors contributed to the ideas in the paper and helped to write, review and revise the manuscript text before submission.

Competing interests

N.F.S. is a co-founder of, has equity in, and has a financial interest with Mosaic ImmunoEngineering Inc. N.S.F. is also a co-founder of, and serves as manager of Pokometz Scientific LLC, under which she is a paid consultant to Flagship Labs 95 Inc. and Arana Biosciences Inc. G.V.L. and J.P.G. received research funding from BASF for topics related to this review. The other authors declare no competing interests.

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