1.1.1 **LABEX ARCANE** (CERMAV, DPM, DCM, SyMMES, LCBM, MEM, LETI)

ARCANE's core theme is chemical design, synthesis and application of novel molecular bioinspired or biosourced architectures as part of translational research into 3 topics related to sustaining and advancing human society: Energy supply, the Environment, and Health. ARCANE partners work toward a common scientific objective: biodriven chemistry, from bioinspiration to biotargeted molecules. This objective relies on a shared scientific vision and complementary know-how. The basic tenet of ARCANE is to take inspiration from Nature to improve Life.

ARCANE was built on 2 **main scientific axes: Bio-Inspired chemistry and Bio-Targeted chemistry**. We intend to keep this structure for the coming decade as it allowed the construction of a creative community which achieved significant breakthroughs. Initially, the 2 scientific axes were supported by 2 methodological axes: physico-chemical characterization and simulation. To enhance the impact of the methodologies developed, forge partnerships with physico-chemists from the Physics, Materials and Engineering department at UGA, and to breathe new life into the 2 scientific axes, we decided to create a third component called the "**Emergence core**". This core will combine physico-chemical characterization and simulation with other methods in synthesis, surface chemistry and hybridization. Its aim is to construct a core of knowledge and know-how feeding into all the interfaces of chemistry in Grenoble and beyond. Details on the expected results, perspectives and outcomes are listed in the Appendix.

1 The research program of the new **Emergence core** will follow 5 tracks: synthesis, surface chemistry, controlled organization and self-assembly, simulation and advanced characterization. The synthesis track aims to establish strategies to synthesize complex natural products, by developing novel synthetic methods for reactivity control (flow chemistry) or one-pot multiple conjugation. Obviously, success on this track will be beneficial for the preparation of tailor-made molecular scaffolds for specific interaction with disease-associated biological targets in the context of chemical biology, for the synthesis of multifunctional molecules (including ligands), and for the preparation of bioinspired compounds. Novel challenges in surface chemistry have emerged related to controllable grafting at every scale of electrocatalytic or photocatalytic molecules. Covalent and non-covalent (supra)molecular techniques must be developed to control the formation of catalyst monolayers, optimize electron transfer and/or provide access to catalytic function. Switching to the nanoscale requires the controlled organization of various nano-objects to maximize (photo)catalytic events (electron transfer, mass transport). Self-assembly of such nanostructures can be controlled by biomolecules (e.g. peptides, protein aggregates, DNA origami). At the macroscale, it is essential to optimize movement of ions and small molecules toward and away from the catalytic site. 3D hierarchical structures will help to control the macroporosity and structure of catalytic layers, and may help stabilize molecules by adapting their environment. The design of molecular multifunctional surfaces is another exciting area which could help promote multifunctional/cascade (photo)catalysis. Probing the organization of hybrid organic/inorganic materials requires the development of dedicated advanced characterization methods and instrumentation. To that aim, we will continue to foster the development of, inter-alia, DNP-enhanced solid state NMR, where Grenoble has a competitive advantage; novel simulation methods to support experimental observations of hybrid systems combining a molecular core in a heterogeneous environment; and methods to predict potentially disruptive catalytic structures.

2 The research program of the **Bio-Targeted axis** will include development of new tools for therapeutic, diagnostic and personalized medicine based on organic chemistry and synthetic biology. New drugs will be synthesized and their biological activity analyzed with the aim of bringing lead

compounds up to the preclinical trial stage. This scientific flow-chart is well mastered within the scope of ARCANE's activity. The drugs themselves will be sourced from plants, particularly Alpine genuses, or designed through mechanistic studies of biological processes. Human diseases (cancer, bacterial, viral and fungal infections, Wilson's, Alzheimer's and other neurodegenerative diseases) will be specifically targeted through the development of multifunctional drugs, synthetic vaccines and new vectorization supports from biosourced materials. In parallel, we will design new molecular tools to help better understand biological processes (telomere maintenance, angiogenesis, etc.). Biotechnology and synthetic biology will be developed through engineered enzymes or bacteria to produce active compounds and glycoconjugated vaccines. We will also develop smart ligands, or synthetic receptors, able to recognize environmentally-relevant molecules such as pollutants or biologically-relevant targets (cancer cells, disease markers), quantify bioanalytes (ions, proteins, nucleic acids) or monitor cell status (redox potential, pH, O_2). Biosensors for pathogen detection or identification of disease-related cell surface modifications will be designed using glycan and lectin microarrays as part of a personalized medicine approach. Biopolymers will be functionalized as injectable hydrogel, matrices for cell cultures or wound healing, and support for vectorization. The development of "bioimaging" tools based on luminescent systems at the molecular (small molecules or peptides) or nano (quantum dots) scale is an emerging research topic that will be promoted. The presence of several imaging platforms in Grenoble, including the X-ray bioimaging platform at ESRF, is a key point for the development of this research topic in collaboration with biologists.

3 Finally, the **Bio-Inspired axis** will build on the achievements from the initial period to foster bioinspiration as a unique tool for innovation in the search for solutions for the energy transition. Thus, we will pursue our efforts to activate small molecules as raw materials and to use sunlight as energy source for more sustainable (solar-driven) chemistry. Specifically, we will focus on complex transformations beyond two-electron transfers such as the production of alcohol, hydrocarbons and ammonia from CO_2 and N_2. Cascade processes will be designed to build complex molecules, mirroring the approach used in synthetic biology. This will involve hybridizing synthetic molecules with biomolecules, extended inorganic solids and possibly living cells. In the field of artificial photosynthesis, we will continue our efforts toward the development of stable and efficient photo(electro)catalytic processes with the aim of establishing the foundations for solar-driven chemistry, mentioned by EUCHEMS as the grand challenge for chemists over the next decades (http://www.euchems.eu/solar-driven-chemistry/). Finally, we will engage in translational research to implement bioinspired catalysts and photocatalysts in operational technological devices, starting with those related to the hydrogen economy for which we have already built prototypes devoid of noble metals. We will investigate factors linked to technological integration, navigate an appropriate learning curve from prototype design, formulation optimization and stability and aging studies, without forgetting socio-economic aspects through adoption of a "safer by design" approach, study of socio-economic and technico-economic impact.

The integration of ARCANE into the CBH-EUR will strengthen collaborations with biologists and help further develop the interface between chemistry and biology, which will benefit and contribute to the success of development of biotargeted systems. In addition, in line with the expected applications in the fields of energy, sensors, molecular devices and catalysts, collaboration with materials scientists and physicists from the LANEF (nanoscience and energy of the future) and CEMAM (Materials science) LABEX will be reinforced and supported.

4.2 PROPOSED 2020-2030 PROGRAM

4.2.1 Emergence core

Expected results and Perspectives	
Synthesis -new efficient and selective synthetic methods for one-pot multiple conjugation -novel modular and convergent strategies for the synthesis of complex natural products or highly functionalized molecules -flow chemistry for controlled reaction of reactive species **Surface Chemistry** -multiscale control of conductive surfaces for bio-inspired catalyst support -the design of molecular multifunctional surfaces -new supramolecular or covalent grafting strategies for molecular engineering **Self-organization processes and outer-sphere control** -directed self-assembly of nanostructures using biomolecules (peptides and nucleic acid, i.e. DNA origami) for new functional materials -promote and analyze catalysis in 3D hierarchical structures at nano, micro and macroscales (Encapsulation in MOFs, protein host, supramolecular cages…; interactions with ionomers…) -improve enzymes/photosystems and bio-inspired systems' stability through the tailoring of environment inside nanostructured supports	**Simulation** -develop new methodologies (reactive force field approach, key-property analysis) to screen novel catalysts and photocatalysts -integration of heterogeneous environment (carbon nanotube, graphene, metal-oxide or quantum dot support) in the modelling of molecular systems -development of combined experimental - computational approaches to solve crystal structures relying on Powder-XRD and (DNP-enhanced) solid-state NMR data -development of multiscale modeling methods, up to very large systems such as whole virus or cell surface, with integration of locally developed structural databases **Advanced characterization** -development of DNP-enhanced NMR methods (including improved polarizing agents) to probe interatomic distances in organic/inorganic materials -development of new hardware (probe, cryostat, laser irradiation, etc.) for improving resolution and sensitivity in NMR -instrumentation for label-free detection: SPR on optical fiber tips, SERS biosensors, ESR mapping of radicals. -development of new sensors such as functionalized chips and electronic noses, and corresponding learning algorithms for pattern recognition **Expected outcomes** -continuous renewal of methodologies to feed the bioinspired and biotargeted axis -development and externalization of novel techniques and methodologies for simulation and characterization -increase interaction with the Physics, Engineering and Materials department of UGA for development of molecular based technologies (molecular electronics and spintronics, sensors…)

4.2.2 Bio-inspired chemistry

Expected results and Perspectives	
Catalysis for energy and sustainable chemistry -detailed understanding and rational control of small molecule activation (O_2, N_2, CO_2, CO, H_2O…) with emphasis on processes involving more than 2 electrons -multi-electronic catalysts with minimal overpotential requirement (high energy conversion efficiency) and high turnover frequency -multi-functional catalysts to perform dual catalysis -implementation of cascade catalysis -polynuclear catalysts to challenge multi-electron catalysis -new (bio)catalytic tools for O, N and S transfer reactions -development of eco-friendly enantioselective catalyses using biomolecules or small multifunctional molecules as asymmetric inductors **Using sunlight to drive chemistry** -low cost, nontoxic, efficient and photosensitizers based on Earth-abundant elements with high stability of their reduced and/or oxidized radical forms (develop push-pull organic dyes to replace Ru-based and related chromophores) -hybrid photocatalysts combining biochemical organic and inorganic moieties as photosensitizers and catalysts -introduce electron storage sites on the photosensitizers to optimize photocatalytic efficiency thanks to light-driven charge photoaccumulation process -use light energy to drive fine chemistry reactions and produce solar fuels (i.e. production of H_2 from water, MeOH or hydrocarbons from CO_2 or NH_3 from N_2)	**Translational energy research** -implement bio-inspired systems into technologically relevant devices through the preparation of molecular-engineered materials -design new hybrid systems with enhanced efficiency by combining the most efficient materials (molecular/inorganic /enzymes…) (Photo)production and refining of fuels via a synthetic biology approach -benchmark performance of catalysts and photocatalysts -understand how heterogeneization and hybridization influences the performances of catalysts and photocatalysts -improve conversion and selectivity of catalytic processes to achieve good energy efficiency -develop noble-metal free catalytic and photosensitive systems as viable technological alternatives -study the mechanisms responsible for low stability and ageing. Develop solutions to overcome these limitations for example through rational control of radical reactivity and ligand design (redox-active ligands) -safer by design: non-toxic and eco-friendly while efficient and stable photosensitizers, catalysts and architectures -develop (electro)chemical and photo(electro) chemical devices to the pre-industrial stage through collaboration with industrial partners and partners from the Physics, Engineering and Materials department of UGA **Expected outcomes** -understand the reactivity of bio-inspired systems by combining low-temperature kinetics, advanced spectroscopy and quantum chemistry -implement bio-inspired systems into technologically relevant devices -develop high power enzymatic or bio-inspired devices (biofuel cells, electrolyzers, photoelectrochemical cells) with enhanced operational lifetimes -improve (photo)catalytic performances through the design of hybrid systems -achieve breakthroughs in driving beyond 2 electrons processes

4.2.3 Bio-targeted chemistry

Expected results and Perspectives	
Bioactive molecules -design, synthesis and development of multifunctional drug candidates for treatment of life threatening diseases -investigation of medicinal plants (with a special focus on alpine plants) as sources of bioactive compounds -exploit metalloenzyme inhibition processes for mechanistically-driven drug design -functionalization of biopolymers as injectable hydrogel, matrices for cell cultures or wound healing and support for vectorization **Synthetic Biology** -biotechnological engineering of molecules with the use of environmentally-friendly synthetic approach -use of metabolically engineered microorganisms to produce active biocompounds such as glycoconjugates vaccines **Targeting and delivery** -functionalized nanoparticles and vectors for tumor targeting -targeted chelation therapy against Wilson & neurodegenerative diseases - development of multivalent biomolecules as anti-infectious and antitumoral agents - design of new vectors based on dual or multi targeting system, for example targeting several transmembrane proteins (integrin receptors, epidermal growth factor receptor (EGFR), neuropilin-1, vascular endothelial growth factor receptor..;) over-expressed in the tumor microenvironment	**Bio-analysis and diagnosis** -development of smart synthetic receptors able to recognize environmentally relevant molecules such as pollutants as well as biologically relevant targets -detection of pathogenic markers (cell microvesicles are indicative for thrombosis, inflammation and metabolic diseases) and corresponding therapeutic monitoring -biomedical imaging (fluorescent and MRI) agents in relation imaging platform and large instruments (ESRF and ILL) -develop theranostic tools for degenerative diseases (Alzeimer, diabetes…) and cancer -microsystems for analysis of individual cells (bacteria, blood samples) -tools for cell dysfunction diagnosis and for detecting various diseases. For example lectin arrays for monitoring aberrant glycosylation on cancer cells -tools such as glyco(dendrimer)arrays for screening and discovery of new antipathogenic agents and immunomodulators **Expected outcomes** - development of panel of theranostic approaches for personalized medicine -bring lead compounds up to the preclinical trials -enhanced knowledge of surface structure and interfacial molecular interactions for applications to functionalized particles, protein-bacteria cell wall interactions… -development of more selective compounds for tumor therapy and detection