Physicochemistry in medicine: some selected examples

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Research on pathological calcifications constitutes an exciting topic at the interface between physics, chemistry and medicine. The relationship between their physicochemical characteristics and the pathology responsible for their formation offers a unique opportunity to perform a significant medical diagnosis, to assess the interaction between drugs and these biological entities as well as to develop new drugs. Regarding synchrotron radiation, the emergence of microbeam allows the clinician to perform an early diagnosis. Indeed, we will start this review with a clinical case where Fourier transform infrared spectroscopy using synchrotron radiation as a probe allowed the clinician to save the kidney function of a patient. Following this example, we will see that investigations on pathological calcifications constitute an elegant way to gather major information on different public health problems such type 2 diabetes as well as on rare diseases. To attain this goal, this mini-review dedicated to structural and chemical investigations and based on selected and recent data collected through techniques using third generation synchrotron radiation as a probe is proposed to the reader.

Keywords: physicochemistry, medicine, pathological calcifications, lithiasis, kidney stones, Randall's plaque, synchrotron, infrared spectroscopy, UV-visible spectroscopy, X-ray fluorescence, X-ray absorption

Introduction

Pathological calcification (PC) occurs frequently in medicine.[1–4] A large part of the literature has tried to demonstrate a causal relationship between PC and pathology. Also, it is worth underlining that controversies exist regarding this link. A well-established relation between calciphylaxis (calcium deposits in the vascular walls) and deleterious consequences such as an increased mortality in affected patients) has been reported in patients suffering end stage renal failure.[5] Gout cases related to the crystallisation of sodium hydrogen urate in synovial fluid are well documented.[6] Renal failure due to crystalline deposits within the kidney was reported in a variety of diseases resulting in the crystallisation of poorly soluble substances excreted by the kidney. Regarding prostate tissue, it is common to find calcium deposits without any obvious relation to the pathology (prostate hypertrophy, adenoma or

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cancer).[7,8] Note that the link between calcification and pathology could be the crystalline species identified within the tissue. For example, breast tumours may be associated with weddellite crystals or with calcium phosphate deposits. It was reported that tumours are benign in the case of calcium oxalate and benign or malignant in the case of calcium phosphate.[9–11]

In the medical literature, papers consider that PCs are made mainly of calcium and distinguish two forms of PC. This dystrophic one occurs in dying and dead tissue. It is well known that injured and dying cells are not able to maintain normal calcium homeostasis, leading to an increase of intracellular calcium levels. The second family, the metastatic calcifications, are associated with elevated extracellular levels of calcium (hypercalcemia), exceeding the homeostatic capacity of cells and tissues. These two definitions are based on the metabolism of calcium. Unfortunately, more than 100 chemical phases have been identified in PC and most of them do not contain calcium.[2,4] Such experimental facts call for another classification based on their pathogenesis process.

We have proposed a more general classification for PC made of three families.[1–4] First, concretions which are found in hollow organs or ducts of the body. For example, kidney stones are solid concretions of dissolved minerals in urine.[12–15] In the case of concretions, crystallisation is induced in metastable supersaturated solutions by spontaneous nucleation when a certain degree of supersaturation is reached (homogeneous nucleation). In contrast, ectopic calcifications are defined as unexpected biomineralisation occurring in soft tissues. It is worth underlining that metastatic and dystrophic calcifications can be considered ectopic calcifications. We may have PCs related to homogeneous and heterogeneous nucleation. This is the case of kidney stones attached at the surface of Randall's plaque (RP). Crystallites in urine (homogeneous nucleation) are agglomerated at the surface of RP which serves as a nucleus (heterogenous nucleation).[16] A third family can be related to physiological calcifications (otoliths, tooth,[17] bone) which becomes pathological with diseases (bone and osteoporosis[18,19]).

In fact, several questions should be answered in the case of crystal deposits within a tissue: what is the accurate composition of the crystal? Is the crystal a specific marker for a pathology? What is the interaction between the crystal and the tissue? Physical methods, including ones implemented on synchrotron facilities, may be of a valuable help to answer all these questions (see, for example, Reference 20).

A clinical case based on synchrotron data

We start this review with the presentation of a clinical case where the characterisation of PC[1–4] through μFT-IR (Fourier transform infrared) spectroscopy performed on the SMIS (Spectroscopy and Microscopy in the Infrared region using Synchrotron) beamline of the SOLEIL (Source Optimisée de Lumière d'Energie Intermédiaire du LURE) Synchrotron plays a pivotal role. A 64-year-old woman was admitted to a nephrology unit for rapidly progressive renal insufficiency with an increased serum creatinine level of about 500 $\mu mol\,L^{-1}$ giving an estimated glomerular filtration rate of 10 $mL\,min^{-1}/1.73\,m^2$. Such a high value for serum creatinine corresponds to a severe impairment of kidney function (normal value >90 $mL\,min^{-1}/1.73\,m^2$). The analysis of her medical file revealed a well-controlled hypertension diagnosed 10 years before as well as a chronic renal failure diagnosed 2 years before with a serum creatinine at 215 $\mu mol\,L^{-1}$. This chronic renal failure was attributed to nephroangiosclerosis, a disease related to hypertension. The fact that this rapidly progressive renal insufficiency failure was not associated to an obvious cause led to a renal biopsy (RB). RB is often necessary for diagnosis, prognostic assessment and therapy guidance of various diseases affecting native and transplanted kidneys.[21] The final diagnosis differs from the main hypothesis in up to one-third of cases.[22] The observation through an optical microscope of the RB shows an extensive tubulo-interstitial fibrosis scattered with multiple small crystallites. For this patient, such observation was definitely not able to determine the chemical nature of these small crystallites (Figure 1.A1).

At this point, it is worth emphasising that more than 20 chemical compounds have been identified including 7 different calcium salts.[23] Thus, the methods used in the hospital setting to gather information on PC in RB are clearly inappropriate. These methods based on staining procedures such as von Kossa staining display some major limitations for the characterisation of ectopic calcifications. It was reported that such staining procedures are not

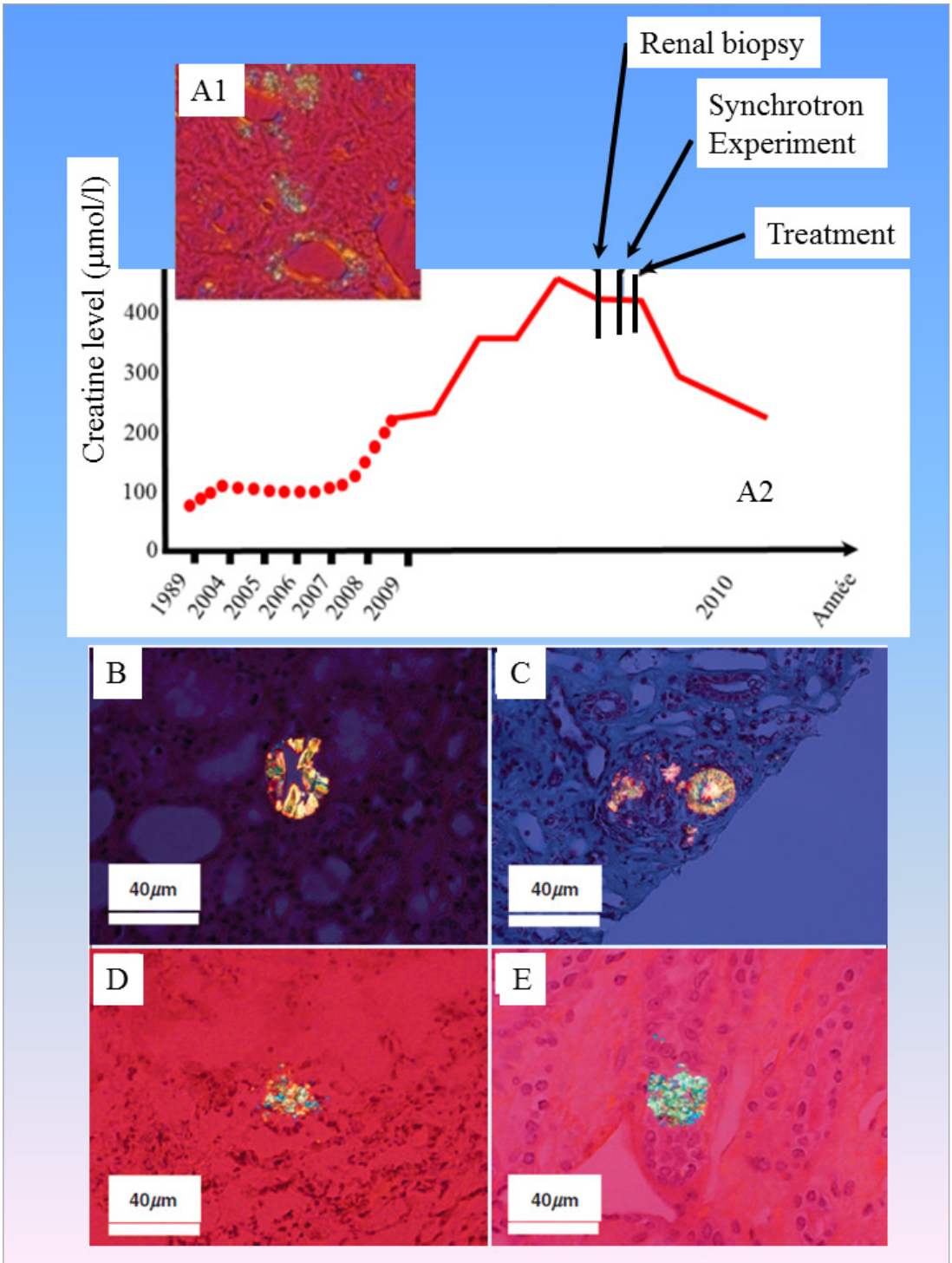

Figure 1. A1, abnormal deposits observed in the tubular cells and interstitium using an optical microscope. A2, evolution of the kidney function as given by the serum creatinine. After a RB, µFT-IR experiments were performed at the SMIS beamline of the SOLEIL Synchrotron. Then, after identifying the crystals as dihydroxyadenine (DHAd), a specific treatment with allopurinol was started and the serum creatinine decreased significantly. In order to illustrate the difficulty to perform a significant medical diagnosis, we show in B and D, whewellite crystallites, while in C and E, DHAd ones are shown. Let us recall that these two chemical phases are related to very different pathologies and thus very different medical treatment. Such similarity calls for a characterisation through a physicochemical technique such µFT-IR spectroscopy.

sufficient for identifying and quantifying apatite to assess bone formation.[24]

Regarding the patient, a genetic investigation is also an option to perform a significant diagnosis. Unfortunately, the cost of such investigation is high. Also, it requires quite a long time. Note that such an approach through genetics must be guided by clinical and biological data. Here an accurate characterisation of the crystals found within the tissue gives key information to the clinician. To identify the chemical nature of the small crystallites, we selected μFT-IR spectroscopy and went to the SMIS beamline of the SOLEIL Synchrotron to perform such an experiment. Quickly, the presence of 2,8-dihydroxyadenine (DHAd) was identified in the kidney biopsy. This compound is produced by the body when it is unable to recycle adenine.[25] This early diagnosis based on synchrotron data made all the difference. The medical treatment (now allopurinol or febuxostat) of the disease thus identified is available and was applied at once. The kidney function of the patient finally recovered. Such diagnosis changed significantly the life of the patient because it was not necessary for her to have dialysis and thus a kidney transplantation. This clinical case has been reported on different websites[26] and published.[27]

From a financial point of view, the cost of an undiagnosed case leading to end stage renal failure is at least 85 k€ per year for dialysis (the average time before kidney transplantation is about 18–24 months), 85 k€ for the kidney graft (around 3100 kidney transplantations per year in France), and finally 10 k€ per year of medical therapy, management of side effects and follow-up of the patient. By comparison, the cost of 8 h synchrotron use to establish a clinically relevant diagnosis is 4 k€ (half an hour is in fact sufficient) while the price of a last generation in-lab μFT-IR spectrometer is around 300 k€ and the cost of an analysis on this equipment is around 160 €. In conclusion, the patient saves her kidney and social security saves some money (more than 350 k€).[28]

Thanks to different state agencies, two in-lab μFT-IR spectrometers allowing us to perform experiments very similar to the one performed on SMIS have been installed at the physiology unit of Tenon Hospital. This clinic case was thus the starting point of a large survey on grafted patients (more than 300 patients are engaged in this investigation) in collaboration with Huriez Hospital, Lille, France. The first patient for which the μFT-IR measurement was performed at Tenon Hospital was a four-year old girl already transplanted and who presented with a kidney graft dysfunction. She had DHAd crystallites present in the RB. Thanks to an early diagnosis of the crystals using μFT-IR spectroscopy, she received allopurinol and she recovered her kidney graft function. At this point, it is worth underlining that since the installation of this apparatus at the Tenon Hospital, 18 patients have been diagnosed with the same pathology.

This preamble shows clearly that PC constitutes an exciting entry point for physicists and chemists in medical research. Regarding the interface between physics and medicine, let us note that the first medical application of X-rays was made by W.C. Röntgen in 1895 through an image of a left hand; this image was in fact the discovery of X-rays. Now, part of the cutting-edge research done in medicine is performed on numerous beamlines implemented on several synchrotron radiation centres.[29–31] At SOLEIL, the French synchrotron facility, the first experiment was performed on kidney stones.[32] Note that a beamline of the European Synchrotron Radiation Facility (ESRF) is dedicated to research in medicine.[33–35]

One of the key points of the research dedicated to PC is linked to the relationship between the pathology which induces such biological entities and their physicochemical characteristics.[12,13,36–38] Such a relationship allows the clinician to establish an early diagnosis and also to develop new drugs.[39] In this review, we would like to present some recent publications related essentially to PC which illustrate the interest of the medical community in synchrotron radiation. To attain this goal, we will start with some generalities regarding PC.[40,41] Then we will present succinctly different techniques, namely X-ray fluorescence,[42] scattering techniques,[43] X-ray absorption spectroscopy,[44,45] FT-IR spectroscopy[46,47] and UV-visible spectroscopy.[48,49] For each characterisation tool, some examples will be given.

Some generalities of PCs

Ubiquity of the PC

PC may occur in various parts of the body, namely kidneys,[12–16] arteries,[50,51] breast,[52–54] gallbladder,[55,56] liver,[57] pancreas,[58,59] prostate,[60,61] saliva,[62] thyroid,[63] heart[64] and cartilage.[65–68] Calcifications may occur also

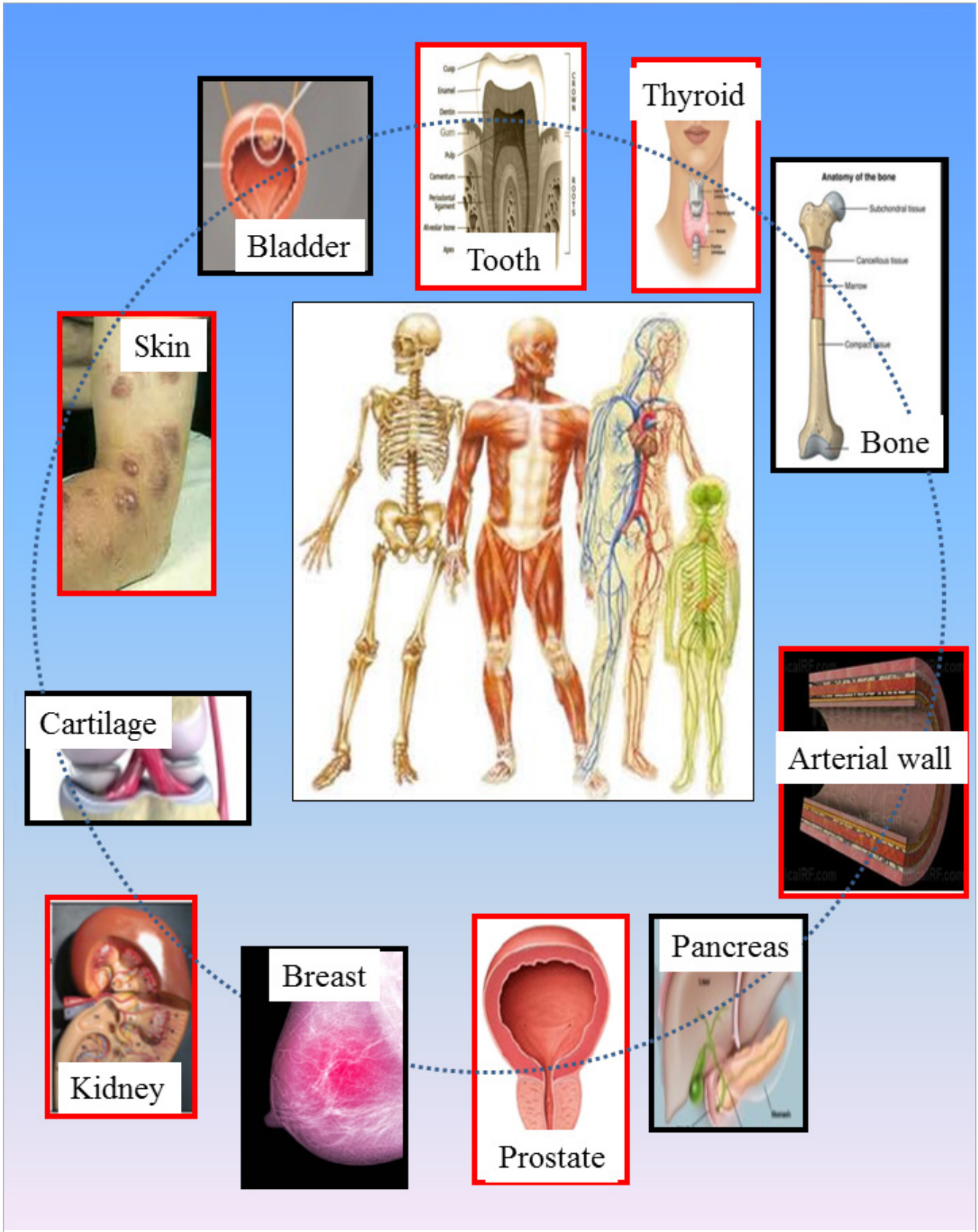

Figure 2. Ubiquity of PC. This figure shows the different locations for the PC we have selected in our research.

on medical devices namely bioprosthetic heart valves,[69] mammary implants,[70] stents[71,72] and intraocular lens.[73] In Figure 2, we present the different organs we have selected for our research on PC. Such approach allows us to assess the different models proposed by the clinician for the pathogenesis of the PC.

For example, in a translational investigation dedicated to the calcifications present in the vessel wall, the data suggest that free DNA coming from cell lysis could be involved in the very first steps of the pathogenesis of these biological entities.[50] The formation of kidney stones is principally related to supersaturation.[12,13] Such considerations demonstrate clearly that only a strong relationship between physico-chemist and physicists may lead to significant breakthroughs.

Finally, such set of samples allows us to consider different types of pathologies and in Figure 3 we show different images obtained on a scanning electron microscope corresponding to kidney infection,[74] breast cancer,[75] iatrogenic[76] and genetic diseases.[77,78]

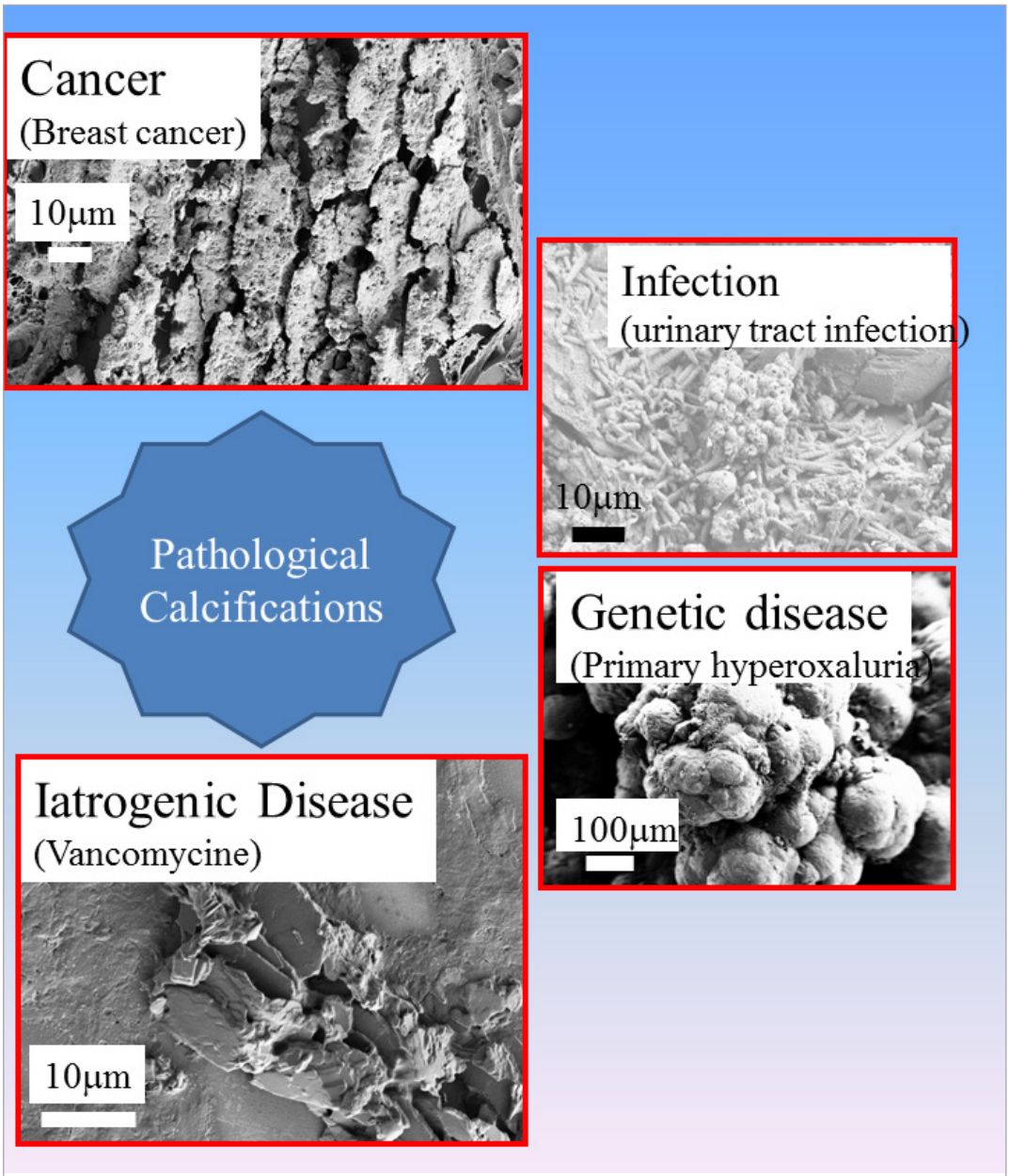

Figure 3. PC are observed for very different pathologies encompassing cancer, infection, genetic disorders and iatrogenic diseases.

A huge chemical diversity

Various medical papers and presentations assume that PC is a lesion in which calcium salts, usually in the form of calcium phosphate with an apatite structure, are deposited abnormally in soft tissues.[79] The analysis of the literature shows that this point does not take into account the huge chemical diversity of these biological entities. Uric acid[80] as well as amino acids such as cystine[81–84] have been identified in PC. Such biological entities may also have an exogenous origin. For example, in kidney, drug-induced renal calculi have been identified[76] and drug crystals in tubules of the kidney have been identified as the cause of kidney injury.[85,86] Other drug crystals responsible for tissue lesions have been reported in the gut.[87] Finally, some silica objects have been identified in the centre of granuloma present in skin and also in kidney stones.[88–91] In a recent publication, following a demand from a dermatologist, we analysed abnormal deposits present on the surface of hairs. We pointed out the presence of titanium dioxide.[92]

Characterisation of PCs

From micrometre scale to nanometre scale

The starting point of this research dedicated to PC has been performed essentially at the micrometre scale using mainly in-lab characterisation techniques.[93,94] More precisely, two characterisation tools have been used namely field emission scanning electron microscopy[23] and μFT-IR spectroscopy.[93] The definition of such approach was made on the basis of the morphoconstitutional model.[12] Then, we begin a physicochemical description at the nanometre scale based on different techniques using synchrotron radiation as a probe.[95] At the nanoscale, major information can be obtained on the pathogenesis of kidney stones.[96,97] In our case, we have used several experimental setups to characterise or mimic the pathogenesis process.[98,99] Among them, let us highlight transmission electron microscopy[97] and nuclear magnetic resonance[100] (Figure 4).

As can be seen in Figure 5, such approach has been used to study Wilson's disease (WD), theranostic vectors, as well as for the interaction between tea and kidney stones. For example, we have proposed an X-ray fluorescence (XRF) spectroscopy-based approach on liver tissue as a diagnostic tool for WD, also known as hepatolenticular degeneration, which is a severe disorder of copper homeostasis caused by mutations in the gene ATP7B encoding a copper-transporting P-type ATPase.[101] Also, a new rapid scan method, Flyscan mode, implemented on the DiffAbs beamline[102] at SOLEIL Synchrotron which allows fast μXRF data acquisition has been used to gather a complete set of data acquired after injection of gold-cluster-enriched mesoporous silica nanospheres, used as potential theranostic vectors, into rats.[103] Finally, we have recently performed a study to assess the possible interaction between green tea, which is widely used as a "healthy" beverage due to its high level of antioxidant polyphenol compounds, and kidney stones made of calcium oxalate. Our data show no evidence for increased stone risk factors or oxalate-dependent stones in daily green tea drinkers.[104]

Fourier transform infrared spectroscopy

FT-IR spectroscopy has been proved to be a powerful characterisation tool for investigations on inorganic as well as organic chemical compounds in both qualitative and quantitative modes.[46,47] This technique is non-destructive and label-free. FT-IR spectroscopy probes vibrational energy levels providing chemical as well as structural information by comparison with database reference spectra.[105–107] The formalism associated with classical μFT-IR spectroscopy indicates that the spatial resolution is limited by the diffraction, its value being around 5 μm. Recently, FT-IR spectroscopy has been combined with atomic force microscopy to break through the diffraction limit leading to a spatial resolution of 20–40 nm.[108,109]

Nowadays, FT-IR spectroscopy is routinely used at several hospitals. Among these, we can cite the characterisation of lipids in graft liver at the Paul Brousse hospital,[110] of concretions and ectopic calcifications in kidney biopsies for 30 years at the Necker hospital and subsequently at the Tenon Hospital.[111,112] Thanks to the morphoconstitutional model,[12] which is a significant relationship between the physicochemical characteristics of urinary stones and the pathology which induces the formation of these biological entities, different epidemiologic breakthroughs have been made.

For example, a specific morphology for apatite kidney stones has been observed in 96.1 % of stones associated

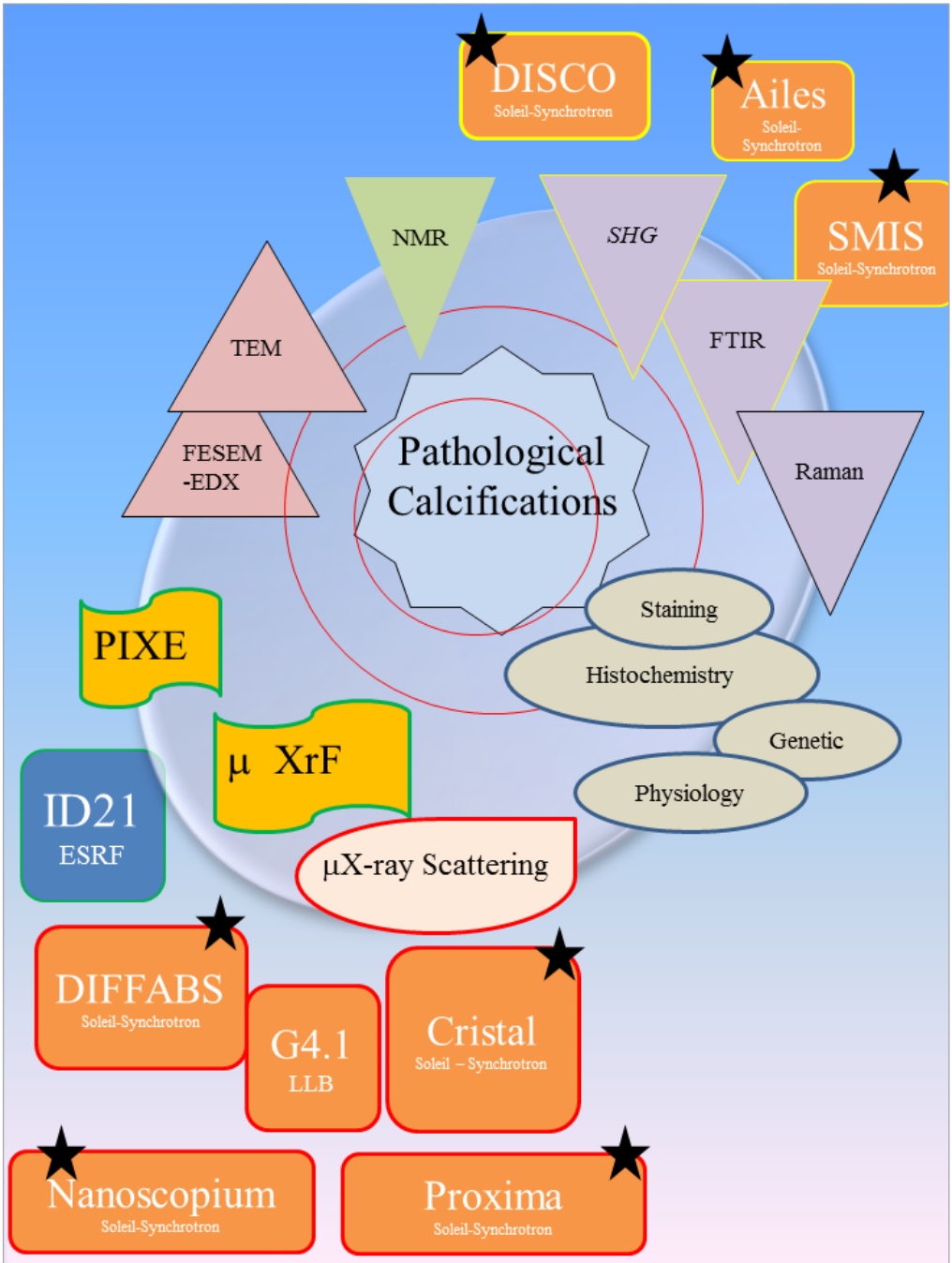

Figure 4. Different experimental devices to characterise PC. Several beamlines implemented at SOLEIL Synchrotron, namely AILES, CRISTAL, DIFFABS, DISCO, NANOSCOPIUM, SMIS have been used. Also, we have used ID21 on the ESRF Synchrotron and G4.1 at the Laboratoire Léon Brillouin (LLB).

with inherited distal renal tubular acidosis.[113] In contrast, other stones of similar composition but different morphologies observed through optical microscopy were related to distal renal tubular acidosis in only 3.9 % of cases. Also, the distribution of the main stone components was analysed in a series of 2464 calculi from 272 (11 %) patients with type 2 diabetes and 2192 without type 2 diabetes. The proportion of uric acid stones was 35.7 % in patients with type 2 diabetes and 11.3 % in patients without type 2 diabetes ($p < 0.0001$).[114] Another example is provided by kidney stones related to infection.[74] FT-IR spectroscopy data have clearly established that

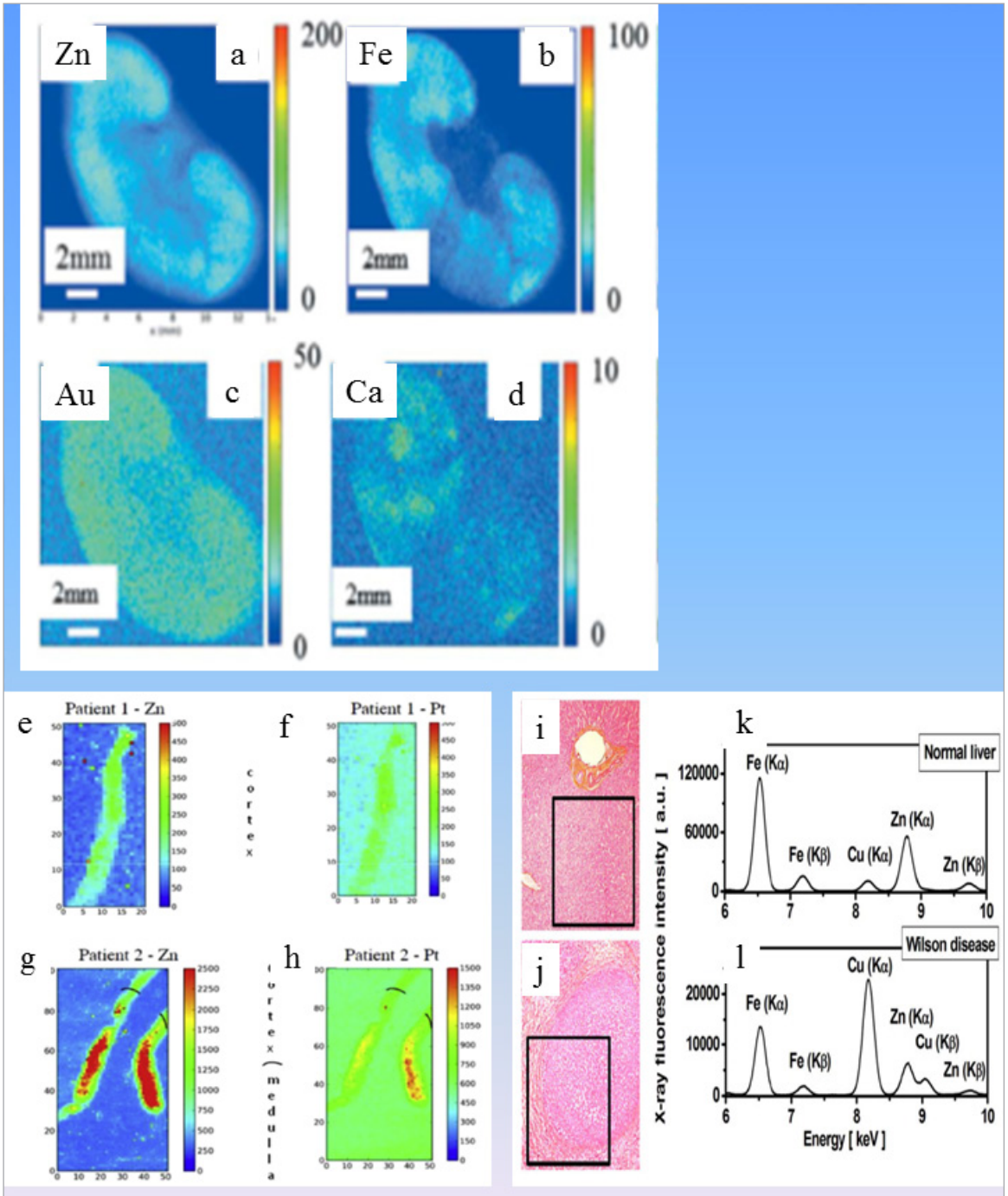

Figure 5. a–d, spatial distribution of different elements, respectively, Zn, Fe, Au, Ca obtained during an investigation of quantum rattle based on gold quantum dots. We can see clearly the mouse's kidney. e–h, spatial distribution of different elements, respectively Zn and Pt, for two patients who received an injection of Pt-based anti-cancer drugs. Statistical analysis of the data allows the clinician to assess inflammation, i–l. For the two samples, classical staining procedures show the samples are not associated with WD, while XRF shows a significant increase of the Cu signal for WD. XRF, thus, constitutes a more sensitive technique than the classical ones and offers the opportunity for the clinician to perform an early diagnostic test.

stones resulting from urinary tract infection due to urea-splitting bacteria consist of calcium phosphate hydroxyapatite admixed with struvite and exhibit a high CO_3^{2-} content.[115,116] Finally, as mentioned previously, several papers show the large chemical diversity of the abnormal deposits in kidney biopsies.[117–119]

In Figure 6, we use the fact that high spatial resolution infrared mapping constitutes a very powerful tool to study the kidney distribution of foscarnet and metabolites. It is well known that foscarnet crystallises in glomeruli.[27] Foscarnet (phosphonoformic acid) is a pyrophosphate analogue that inhibits the DNA polymerase of all herpes viruses. Foscarnet is commonly used in immuno-suppressed patients (AIDS, grafted patients) who have developed cytomegalovirus infection. Through µFT-IR performed on the SMIS beamline, we confirmed the presence of sodium foscarnet crystals in glomeruli. In addition, we found in the cells of the proximal tubule a deposit made of calcium phosphate apatite. Such experimental data suggest that the drug is locally metabolised by splitting the bond between the two phosphate residues of foscarnet. To the best of our knowledge, no experimental data has been reported about crystalline or amorphous chemical phases deposited within the cells of the tubules in the kidney.

UV-visible spectroscopy

We discuss another, recent clinical case already presented at a conference.[120] A 7-month old child, who did not present any comorbidities, developed an end stage renal failure of unclear origin. The first retained diagnosis was acute tubular necrosis secondary to acute dehydration in a context of sepsis. Renal ultrasound showed two well-differentiated kidneys measuring 57 mm and 69 mm.

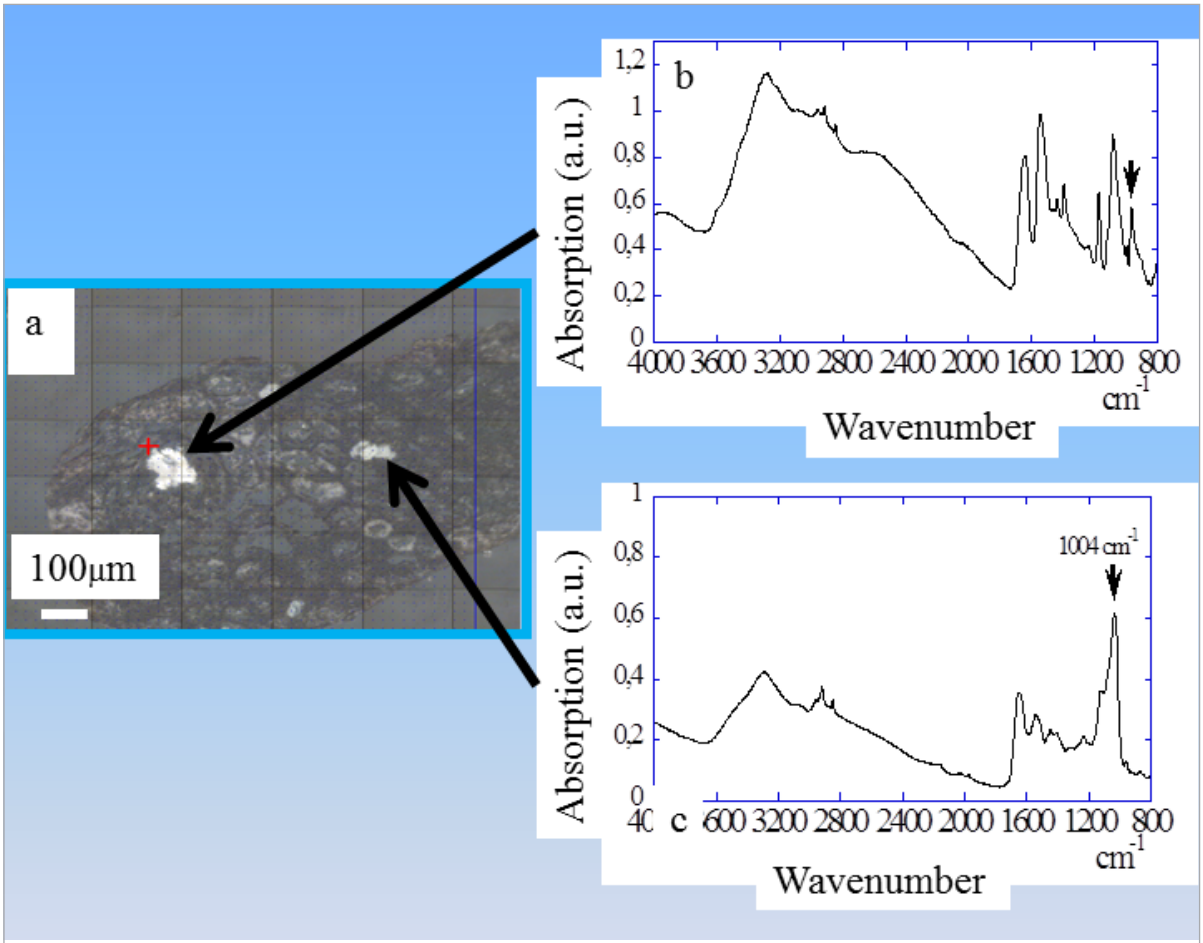

Figure 6. a, optical image of a birefringent structure positioned in glomeruli. b, µFT-IR spectra shows clearly the presence of sodium foscarnet in glomeruli. c, µFT-IR spectra shows clearly the presence of apatite in the cells of the proximal tubule.

There was no evidence of malformation or obstruction. The cortex was slightly hyperechogenic. Parents are not related and they are no known nephropathies in the family.

Since she did not recover her kidney function, a biopsy was performed five weeks after acute renal failure. It revealed tubular impairment with few signs of regeneration and persistence of a discrete inflammatory infiltrate made of lymphocytes and macrophages. They were no glomerular nor vascular lesions. By microscopic examination under polarised light, only three small (<10 µm) intracellular birefringent crystals were found in the tubules (Figure 7a). Infrared microscopy using our PerkinElmer infrared spectrometer and synchrotron radiation (SMIS beamline) were performed to identify the crystals, but the results were inconclusive.

Then, we started an investigation on the DISCO beamline.[118,121] We started by considering macroscopic kidney stones made of calcium oxalate monohydrate (COM). The spectrum of these kidney stones has a specific signal around 410 nm. Then, we came back to the microcrystals present in tissues for the patient discussed just above. The spectrum obtained for the biopsy was very similar to that of the kidney stones made of COM, suggesting that the microcrystals were also made of COM (Figure 7b). Finally, we used this specific signal to obtain the distribution of oxalate in tissue (Figure 7c). Surprisingly, we observed a positive signal in almost 50 % of the tubular cells. Such observation takes into account that while IR spectroscopy is sensitive only to oxalate linked to calcium, UV-visible spectroscopy offers the possibility to gather information on oxalate linked or not to calcium. UV-visible spectroscopy opens the way to a completely new paradigm regarding ectopic calcifications. Further work is in progress on a larger number of samples.

X-ray fluorescence

In the photoelectric absorption process, the absorption of incident photons leads to the ejection of photoelectrons if the photon energy is sufficient. The atomic relaxation

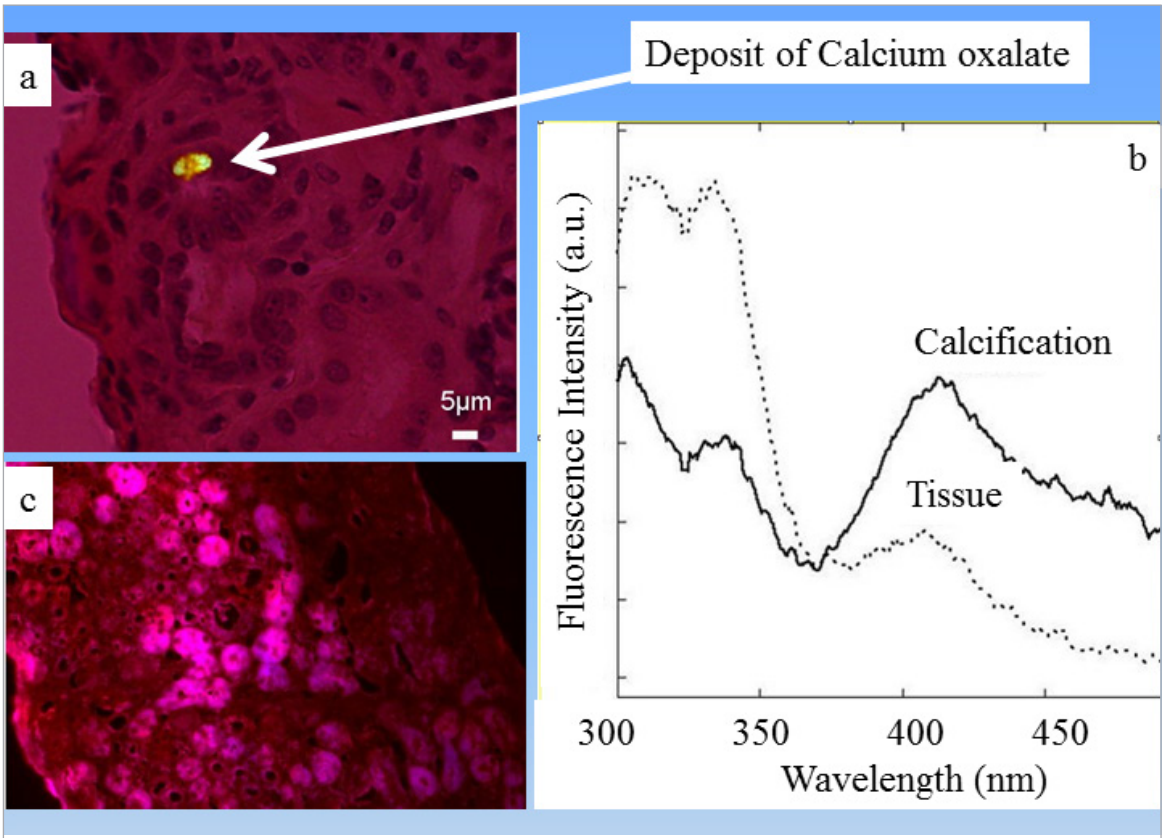

Figure 7. a, optical image of a birefringent structure. b, UV-visible spectra related to this abnormal deposit. c, spatial distribution of oxalate in the tissue obtained through UV-visible data.

process produce XRF radiation with characteristic energies of the atom and also other photoelectrons called Auger electrons.[42] The characteristic energies of the XRF radiation emitted from a sample offer the opportunity to identify unambiguously and quantify the different elements present.

This technique has been used to characterise different kinds of PC.[122–125] First, note that investigation of calcification chemistry is hampered by the difficulty of quickly and systematically locating sites. A recent publication shows that XRF spectroscopy can be used to locate micro-calcifications within tissue specimens.[126] Exciting results have been obtained on the ultrastructure of vascular calcifications in uremia. The complete set of data suggests that uremic micro-calcifications originate from nanocrystals, are chemically diverse and intimately associate with proteinaceous inhibitors of calcification.[127] Furthermore, considering the core-shell structure of the calcifications, apoptotic bodies or matrix vesicles may serve as a calcification nidus. In another investigation, the authors examine the presence of Zn, a trace element, in osteoarthritis (OA) cartilage and meniscus from patients undergoing total knee joint replacement for primary OA.[128] A fine analysis of the data seems to show that Zn^{2+} cations present in the cartilage belong to two chemical species. The first may correspond to Zn^{2+} embedded in protein (several Zn metalloproteins are known to prevent calcification in biological tissues). The second may be associated with a Zn^{2+} trapped in or at the surface of the calcification.[128] Calcification present in OA cartilage may significantly modify the spatial distribution of Zn^{2+}, part of the Zn may be trapped in the calcification and may alter the associated biological function of Zn^{2+} metalloproteins. Finally, synchrotron-radiation-induced μXRF analyses can be used to investigate the distribution of Pb in human joints.[129] The X-ray absorption near-edge structure (XANES) spectra collected at the Pb L_{III} edge for a microbeam positioned at the tidemark and at the trabecular bone were found to be highly correlated with the spectra of synthetic Pb-doped carbonated hydroxyapatite. The authors suggest that in both of these very different tissues Pb is incorporated into the hydroxyapatite structure.

Obviously, XRF has other medical applications. In our case, we have used XRF to investigate the spatial distribution of platinum-based drugs. These molecules are widely employed as anti-cancer agents because of their efficacy against a variety of tumours, but their use is limited by their nephrotoxicity.[130] In the first part with a dedicated focus on mice, the cisplatin injection induced a redistribution of medullary Zn across the corticomedullary junction where histological lesions develop. These results were confirmed by a quantitative approach based on an evaluation of Pearson's and Manders' co-localisation coefficients. The data suggest that the spatial distribution of Zn^{2+} cations and more precisely its correlation with platinum can be used to evaluate the nephrotoxicity of cisplatin. This could lead to new diagnosis, physiopathological and even therapeutical approaches.[131] Regarding the investigation on human biopsy, we were able to discuss the spatial repartition of Pt and Zn in RB. Therefore, μXRF could also be of major interest to decipher the mechanism beyond Pt-induced neurotoxicity, ototoxicity on human biopsy.[132]

X-ray absorption spectroscopy (XAS)

Due to its ability to give structural and electronic information on materials without long range order, such as clusters or molecules,[44,45,133–135] XAS has made major contributions to a wide variety of medical research topics.[136,137] More precisely, C.M. Weekley *et al.* have combined XAS and XRF techniques to assess the problem of selenium speciation in biological systems.[138] More recently, XAS experiments have brought major information regarding a progressive neurodegenerative disease, namely Friedreich's ataxia.[139]

XAS is a direct probe of atomic distribution via electron diffraction. One of the key successes of XAS comes from the fact that last generation synchrotron sources provide a range of X-ray energies with a microbeam that are applicable to most elements in the Periodic Table.

More precisely, we may distinguish two parts of the X-ray absorption spectrum: XANES and extended X-ray absorption fine structure (EXAFS).[44,45] XANES corresponds to the measurement of transitions from core electronic states of the metal to the excited electronic states, while EXAFS corresponds to a transition to the continuum. XANES and EXAFS spectroscopies give complementary structural and electronic information. The XANES part describes the electronic structure and symmetry of the metal site, while the EXAFS part gives

a fine description of numbers, types and distances to neighbouring atoms from the absorbing element. Note that for nanometre scale metallic cluster, EXAFS spectroscopy is insensitive to polydispersity.[140]

Regarding kidney stones, the study of RP constitutes a major research topic. Based on extensive forensic studies performed on kidney between 1935 and 1938, A. Randall, an American urologist, observed, at the tip of the renal papillae, an abnormal deposit of calcium phosphate (named RP).[141] A precise observation of these RPs indicate that these PCs serve as a nidus of kidney stones.[142,143] As this point, it is worth underlining that calcium oxalate stone incidence has increased worldwide during the past decades.[143,144] The observation that a growing number of kidney stones are related to RP has motivated a large number of investigations based on last generation characterisation techniques (see, for example, recent References 145 and 146).

Through XAS performed at the Ca K-absorption edge, a technique specific to synchrotron radiation (Figure 8), the presence and crystallinity of the Ca phosphate phases present in RP were determined *ex vivo*.[147] Direct structural evidence of the presence of amorphous carbonated calcium phosphate (ACCP) as a major constituent is given for the first time. This set of XANES data obtained on *ex vivo* samples, coherent with previous studies performed on RP extracted from kidney stones, shows that this chemical phase can be considered as one precursor in the genesis of RP. From a biochemical

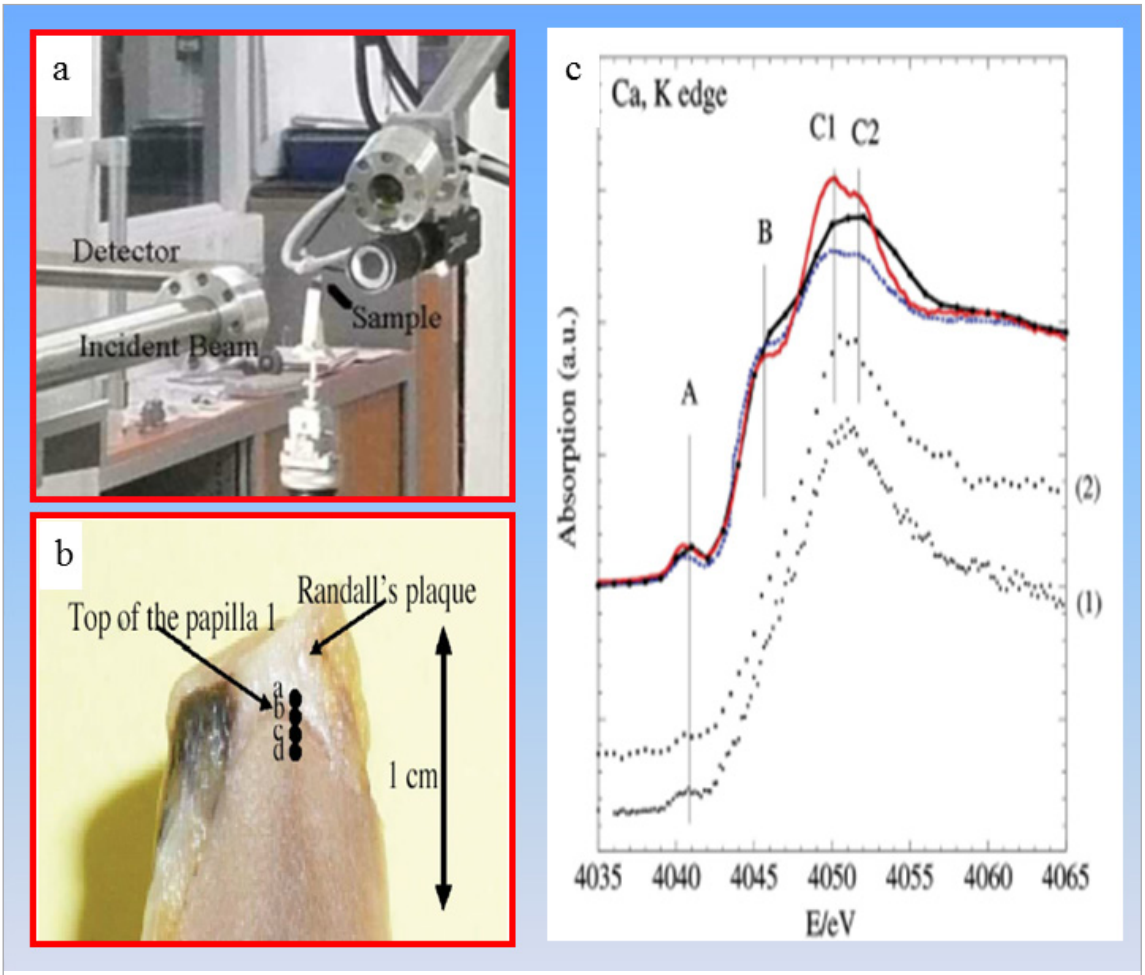

Figure 8. a, photograph of the DIFFABS beamline. b, photograph of the RP positioned at the top of the papilla. c, XANES spectra at the Ca K-edge of two RPs (dotted lines) is compared to reference compounds; synthetic well-crystallised stoichiometric Ca phosphate apatite (HAP, red curve), crystallised biological Ca phosphate apatite (CA, blue dots) exhibiting nm-sized crystals, amorphous carbonated calcium phosphate (ACCP, black curve with circles).

point of view, it is worth pointing out that in the kidney ACCP is considered as evidence of an oversaturation in Ca phosphate by an excess of Ca and/or phosphate and/or due to a too high pH. Such chemical compositions of RP present in increasingly young subjects raises a major question regarding public alimentation: does nutrient-enriched food with calcium and vitamin D specially aimed at young children affect the physiology of the kidney? The question is open.[148,149]

X-ray and neutron scattering

Since the first experiment carried out using a classical vacuum tube at the beginning of the previous century, X-ray diffraction (XRD) has emerged to be one of the most powerful characterisation techniques in almost every field of science and technology. Many books and several review articles have been dedicated to the numerous methods of characterisation linked to X-ray scattering.[43,150] Basically, scattering techniques can be used either to determine the crystal structure or the chemical composition of the samples through the powder diffraction bank data file. As previously underlined, FT-IR spectroscopy can also give the chemical composition, but XRD and FT-IR display advantages as well as limitations. XRD gives the size of the crystal for each chemical phase which are identified, but this technique is only sensitive to chemical phases with long range order.[43] FT-IR is sensitive to amorphous and crystallised compounds and gives some important structural characteristics such as the carbonate level of apatite. This structural characteristic is of major importance to establish a possible infection involved in stone formation.

Regarding kidney stones, we have used scattering techniques to determine structural characteristics of different unknown chemical phases present in kidney stones.[151–153] The identification of a new compound in kidney stones is relevant in clinical practice. Such a new chemical phase is often related to a new kidney disease.

In order to determine the crystal's size in the case of kidney stones made of COM,[154] cystine[83] and uric acid,[155] we have used neutron scattering.[156] More generally, because neutrons do not significantly damage biological solids such as kidney stones, they offer the opportunity to investigate bulk biological samples, whether as an aqueous solution, a solid, a powder or a crystal. Neutron scattering uniquely complements other characterisation techniques, and together with X-ray synchrotron analysis, is considered among the most useful microscopic probes of matter available today.[157] Unlike X-rays, they do not interact with the electronic cloud of an atom, but with its nucleus: the strength and character of this neutron–nucleus interaction is characterised by the so-called neutron scattering length. This neutron scattering length varies irregularly from one nucleus to another. In particular, this parameter is quite significant for light elements like hydrogen, carbon, nitrogen or oxygen, which are almost invisible to X-rays. Neutrons like photons and electrons constitute thus an important probe in the investigation of the matter and especially in the location and dynamics of protons, an essential aspect in many biological processes.

Among the different key results we have obtained using neutrons as a probe, we will discuss the ones related to uric acid kidney stones.[155] As noticed previously, recent epidemiological investigations have identified an association between type 2 diabetes and uric acid kidney stones.[114,155] Such a relationship is more apparent in women than in men. Through powder neutron diffraction,[156,157] we have shown that particle sizes of uric acid kidney stones were significantly different between male and female patients (84.7 nm ± 5.3 nm vs 140.2 nm ± 6.7 nm, $p = 0.000003$). When we consider male and female patients with type 2 diabetes, this structural difference between male and female vanished (76.1 nm ± 3.9 nm vs 78.8 nm ± 4.2 nm, not significant). We try to explain these structural data obtained on kidney stones and based on neutron scattering experiment, in line with observations regarding epidemiological data on arguments based on supersaturation.

Conclusion and perspectives

This mini-review dedicated to research performed on PC shows clearly an exciting meeting between physics, chemistry and medicine. Due the complexity of such biological entities which contain organic and inorganic parts in which trace elements are present, different in-lab characterisation techniques are used. Analysis at the micrometre scale is carried out by techniques using synchrotron radiation as a probe, which gives the opportunity to describe the structural characteristics of human calcification at the nanometre scale. Note that we have also performed very exciting investigations

on cells[158] and mice.[84,131,159–161] Finally, it is worth underlining that fundamental research performed on the adsorption of molecules on clusters is also carried out.[162–165] Such a fundamental approach will help us to understand how molecules interact with nanocrystals and modify their morphology.

In conclusion, results obtained with synchrotron radiation have been used to develop new diagnostic methods and to understand more deeply the pathogenesis process of PC. Second, a technology transfer has been done in order to perform similar experiments at the hospital. It is worth underlining that more than 1600 kidney biopsies have been characterised following the publication in *PLoS ONE* dedicated to kidney biopsies in close collaboration with SOLEIL Synchrotron.[27] To attain this goal, we performed the measurements with young doctors, namely Dr E. Bouderlique (Nephrologist), Dr F. Brunet-Possenti (Dermatologist), Dr X. Carpentier (Urologist), Dr R. Coscas (Cardiologist), Dr H. Colboc (Dermatologist), Dr E. Estève (Nephrologist), Dr A. Gauffenik (Rheumatologist), Dr J. Guerlain (Otorhinolaryngologist), Dr R. Kormann (Nephrologist), Dr M. Livrozet (Nephrologist), Dr Y. Luque (Nephrologist), Dr Ch. Nguyen (Rheumatologist), Dr B. Pradère (Urologist), Dr C. St Jacques (Nephrologist), Dr C. Verrier (Urologist) and Dr V. Masson-Behar (Rheumatologist), who finally have the opportunity to define completely new research topics.

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